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AGRANULOCYTIC ANGINA FOLLOWING CHLORPROMAZINE (LARGACTIL)

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Attention has not been drawn to the occurrence of agranulocytic angina following chlorpromazine in South Africa, although the condition has recently been reported elsewhere. Since the drug is widely employed in practice, and many believe it to be harmless, a case is recorded and discussed.

CASE REPORT

A woman of 62 years, seen for the first time on 31 December 1954, had suffered the loss of her husband 4 years ago. She had in consequence many anxieties, had become very depressed, and had at times entertained suicidal ideas—'death seemed to hold no terrors'—and thought that she would be better dead. She was always recalling unhappy memories and past errors. Severe insomnia developed and she would wake up unrefreshed each morning with a feeling of impending disaster. All work seemed a considerable effort. 'Sinking feelings in the abdomen', when her 'stomach always seemed to be knotted up', occurred as well. Her appetite was poor. Some pressure sensations in the head were experienced; otherwise she was symptom-free.

Physical examination revealed a blood pressure of 215/80 mm. Hg. A slight systolic murmur was present at the aortic area. There were no other pathological signs in the cardiovascular system and no abnormalities in the respiratory, nervous and gastro-intestinal systems. Screening of the chest revealed a tortuous aorta, but the heart was not enlarged. An electrocardiogram showed no abnormality.

Several practitioners had treated her, originally with Vegolysen for about a year, and subsequently with Serpasil. Three weeks previously the Serpasil had been discontinued and some other medication supplied. At this time she developed an acute exacerbation of all her symptoms and felt very much more depressed and very much more fatigued than previously.

On 31 December 1954 Largactil, 25 mg. *t.i.d.* was prescribed. A week later the dose was increased to 50 mg. *t.i.d.* and on 26 January 1955 the dose was again increased to 200 mg. a day (3 25-mg. tablets in the morning, 2 after lunch and 3 at night). The patient received in addition 1 tablet (5 mg.) of Dexedrine daily after breakfast and also at times 3 gr. of Tuinal at night.

Her condition improved remarkably. All symptoms subsided, depression vanished and she felt refreshed after sleep; 'life became worth living', and all thoughts of suicide disappeared. However, this satisfactory course was not to be maintained. On 21 March the patient complained of a sore throat which had been present for a week. At this time she looked very ill, the temperature was 101°F and the pharynx was very reddened and markedly swollen on both sides.

Blood Picture. A white-cell count (performed by Dr. B. Sampson) revealed that there was a total of only 900 white cells per c.mm. Of these 14% were polymorphonuclears, 84% lymphocytes and 2% monocytes. On 23 March a second blood investigation (performed by Dr. L. Walker) revealed: haemoglobin 13.5 g. (95%), red cells 4·63 m. per c.mm., colour index 1·03, total white cells 1,300 per c.mm. (polymorphonuclears 9%, lymphocytes 67%, monocytes 18% and metamyelocytes 6%).

Examination of the sternal marrow by Dr. Walker on 24 March showed the following: 'Total nucleated count—17,000 per c.mm. Numerous marrow particles were aspirated from the sternum and the impression gained from examination of these was that the marrow was of normal cellularity. Differential count (on 500 cells): myeloblasts 0·2%, promyelocytes 0·2%, myelocytes 8·4%, metamyelocytes 1·0%, polymorphonuclears 2·4%, staff cells 0·2%, lymphocytes 14·4%, monocytes 0·2%, plasma cells 3·4%, pro-erythroblasts 1·0%, erythroblasts 27·0%, normoblasts 39·4%, unidentified 2·0%, megakaryocytes 0·2%. Erythroid: myeloid ratio 5·4 : 1. The majority of the cells in this marrow showed toxic changes. The nuclei stained more pyknotically than usual, and identification was difficult at times. Megakaryocytes and platelets appeared to be between normal and increased in numbers. Plasma cells were increased. The most prominent cell-types were of the erythroid series and the granular series were markedly deficient in numbers. These findings confirm the diagnosis of agranulocytosis. There is no evidence of leukaemia, and neoplastic cells were not seen'.

The chlorpromazine was immediately discontinued and the patient treated with penicillin (2·4 m. units of procaine penicillin daily), streptomycin (1 g. *b.d.*), terramycin (2 g. daily) and cortisone (300 mg. a day). The temperature began to subside on the 4th day, after the dose of penicillin had been raised to 4·8 m. units a day. The patient was symptom-free by the end of the first week and made a good recovery.

By 12 April (at which time the patient had a small pustule on the nose) the white cell count was 11,800 per c.mm. (polymorphonuclears 80%, lymphocytes 19%, monocytes 1%). The subsequent course has been uneventful.

DISCUSSION

A severely depressed woman of 62 years improving remarkably when chlorpromazine was administered, developed agranulocytic angina. She had also been receiving Dexedrine and Tuinal but both these drugs have since been administered to her without any ill effect. It is therefore believed that the chlorpromazine caused the bone-marrow depression.

Very few communications on the subject have as yet been published. Tasker[1] reviewed the cases which had come to his notice and added one of his own, making

a total of 4 recorded cases at the time that he wrote his article. A further case was reported by Prokopowycz.[2] Tasker's case was that of a married woman of 38 years; all the other patients were middle-aged or elderly women. In one instance dermatitis, and in one jaundice and dermatitis, preceded the agranulocytosis, which in these reported cases tended to occur at about the 6th week of chlorpromazine therapy. Two of these patients (Tasker's and Prokopowycz's) died; both were given antibiotics but not cortisone or ACTH. Of the 3 cases which recovered, one received cortisone and the others were treated with penicillin and blood transfusion.

Goldman[3] in a brief account of this complication mentioned that agranulocytosis occurred in 3 out of about 500 patients to whom chlorpromazine had been administered. His 3 patients—all of whom recovered—were given corticotrophin-gel intramuscularly in doses of 40 units twice a day; corticotrophin, 40 units intravenously for the first 3 days; and penicillin, 1-2 million units daily. In 2 of these cases tetracycline was also administered.

In the case recorded in this paper, agranulocytosis did not develop until the patient had been exposed to chlorpromazine for about 3 months, and until a total of about 14 g. had been administered. Premonitory toxic symptoms such as dermatitis did not precede the agranulocytosis. Antibiotic saturation was practised in view of the gravity of the disease, while large doses of cortisone were also administered.

Of the cases recorded to date (including the case here described), all 5 patients who received cortisone or ACTH recovered. In the group of 4 who did not receive cortisone or ACTH there were 2 deaths. While these numbers are very small, the difference should be borne in mind until a larger series of cases is available.

SUMMARY

A further case of agranulocytosis following chlorpromazine is reported.

All cases in which details were available occurred in women. The youngest patient was 38 years of age.

The case reported here recovered after chlorpromazine had been withheld and after massive doses of antibiotics and large doses of cortisone had been administered; therapy on these lines is perhaps the treatment of choice at present.

REFERENCES

1. Tasker, J. R. (1955): Brit. Med. J., **1**, 950.
2. Prokopowycz, V. (1955): J. Amer. Med. Assoc., **157**, 1042.
3. Goldman, D. (1955): *Ibid.*, **157**, 1274.

QUESTIONS ANSWERED

COENURUS CEREBRALIS IN THE HUMAN BRAIN

Q. A correspondent in a letter published in this issue on page 696 describes a case of this condition and asks about the incidence of *Coenurus cerebralis* in South Africa.

A. Parasitic infestation of the human brain by *Coenurus cerebralis* is not uncommon in South Africa and P. J. P. Becker and S. Jacobson have recorded 4 proved cases.[1]

Briefly, the parasite is the larval stage of the tapeworm *Multiceps multiceps* which is an intestinal parasite of dogs. The larval form may be found in the brain and spinal cord of sheep, goats, cattle, horses, antelopes and monkeys—and man is also an occasional intermediate host, especially in sheep-farming areas, where dogs are kept as pets or to guard the sheep. In sheep the characteristic manifestation is 'gid' (giddiness or vertigo). Man may become infected by contamination with dog's faeces and the larvae (coenurus) invades the central nervous system, where they tend to lodge, especially in the cerebospinal fluid pathways. Diagnosis usually rests on the following points:

(1) Headache of long duration with or without epilepsy.

(2) Variability of cerebral neurological signs.

(3) Eventual severe papilloedema.

(4) Increased pressure of cerebospinal fluid, increased protein and almost invariably a cellular response in the C.S.F.

(5) History of association with both sheep and dogs.

Pathological diagnosis rests on demonstrating the characteristic morphological features of the coenurus and its scolices. This may not be easy as the human brain is not an ideal medium and many of the cysts become sterile.

We are certain that the condition is far commoner in South Africa than has been supposed.

1. Becker, P. J. P. and Jacobson, S. (1951): Lancet, **2**, 198 and 1202.

ASSOCIATION NEWS : VERENIGINGSNUUS

Medical Aid Societies. Medical Aid Societies, especially those with members all over the Union, have reported that medical practitioners often fail to give the home or business address of the patient when advising societies that accounts of members of societies are overdue, as instructed at the end of paragraph 2 on page 1 of the Tariff Book.

It would be appreciated if practitioners would give the business address rather than the home address as it would facilitate tracing the member when there are more than one of the same name and possibly with the same initials in the society.

L. M. Marchand
Associate Secretary

Medical House
Cape Town
1 July 1955

Mediese Hulpverenigings. Mediese Hulpverenigings, veral die met lede in alle dele van die Unie, rapporteer dat geneeshere dikwels versuim om die huis- of besigheidsadres van die pasiënt te meld wanneer hul die verenigings in kennis stel dat lede se rekenings nog nie betaal is nie, soos aan die einde van paragraaf 2 op bladsy 1 van die Tariefboek aangedui word.

Dit sal op prys gestel word as geneeshere eerder die besigheidsadres as die huisadres aangee; dan sal dit makliker wees om die lid op te spoor as die vereniging meer as een lid met dieselfde naam en moontlik met dieselfde voorletters op hul boeke het.

L. M. Marchand
Medesekretaris

Mediese Huis
Kaapstad
1 Julie 1955

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EDITORIAL

THE COMET DISASTERS

On 10 January 1954 a *Comet* took off from Rome for London and crashed into the sea, after a loud explosion, near Elba. Three months later, on 8 April 1954, a Cairo-bound *Comet* from Rome disappeared into the sea near Naples. The British Overseas Airways Corporation immediately grounded all its *Comets* and instituted an intensive official investigation into the cause of the disaster. Salvage operations, undertaken off Elba, eventually yielded wreckage from which aeronautical experts could speculate on the possible mechanical diagnosis of the cause of the disaster; but the Elba wreckage was very incomplete and the sea was too deep off Naples to retrieve anything at all, so that great store was placed on the medical evidence. Fifteen bodies were found near the Elba disaster, and 6 were fished from the sea off Naples.

A report of the findings, research and conclusions of the medical investigators has been published in *The Lancet* of 4 June 1955.[1] The post-mortem examinations were performed by an eminent Italian forensic pathologist, and tissue sections were studied subsequently at the Royal Air Force Institute of Aviation Medicine at Farnborough, England, where animal and mechanical experiments were also carried out. The pattern of injury discovered at post-mortem examination was remarkably uniform on all the bodies; it seemed to indicate from the start that the mechanism of death, or the sequence of events leading to it, was the same for all the occupants irrespective of individual factors such as the location of seats in the cabin and the amount and type of clothing that each was wearing. In a typical case the following lesions were found: Ante-mortem fractures of the skull; disruption of the thoracic cage either by spinal fracture or by costo-vertebral dislocation; post-mortem fractures of the limbs; severe injury to the lungs with haemothorax, and to the heart, which was either ruptured or torn from the great vessels; haemoperitoneum with lacerated liver and/or spleen; and, finally, peculiar skin changes.

The chest injuries provided the best clues to the probable sequel of traumatic events. The pulmonary

VAN DIE REDAKSIE

DIE COMET-RAMPE

Op 10 Januarie 1954 het 'n *Comet* van Rome na Londen vertrek en na 'n geweldige ontploffing naby Elba in die see gestort. Drie maande later, op 8 April 1954, het nog 'n *Comet* in sy vlug van Rome na Kaïro naby Napels in die see gestort en verdwyn. Die *British Overseas Airways Corporation* het onmiddellik al hul *Comets* buite diens gestel en 'n intensiewe amptelike ondersoek na die oorsaak van die lugrampe ingestel. Berging naby Elba het uiteindelik wrakgoedere opgelewer op grond waarvan lugvaartkundiges sekere berekeninge omtrent die moontlike meganiese oorsaak van die ongeluk kon maak. Omdat die Elba-wrak egter baie onvolledig was en die see by Napels te diep was om enigiets te berg, is groot waarde aan die mediese bevinding geheg. Vyftien lyke is naby die toneel van die Elba-wrak gevind, en 6 is by Napels uit die see gehaal.

'n Verslag van die bevindings, navorsing en gevolgtrekkings van die mediese navorsers het in *The Lancet* op 4 Junie 1955[1] verskyn. 'n Vooraanstaande Italiaanse geregtelike patoloog het die lykskouings waargeneem, en by die *Royal Air Force Institute of Aviation Medicine* te Farnborough, Engeland, is die weefseldeursnitte later bestudeer. Hier is ook eksperimente, meganies en met diere, gedoen. By die lykskouing is bevind dat die letselpatrone opvallend eenders was op al die liggame. Uit die staanspoor het hierdie feit daarop gedui dat die doodsmeganisme, of die opvolging van gebeurtenisse wat tot die dood gelei het, dieselfde was in die geval van elke passasier, ondanks individuele faktore soos die posisie van sitplekke of elkeen se hoeveelheid en soort kleredrag. Die volgende letsels is in 'n kenmerkende geval opgedoen: voordoodse breuke van die skedel; uiteenskeuring van die borskas òf deur 'n breuk in die ruggraat òf rib-ruggraatontwrigting; nadoodse breuke van die ledemate; ernstige verwonding van die longe gepaard met borsholtebloeding, en ook van die hart wat òf geskeur was òf van die groot bloedvate losgeruk was; bloeduitstorting in die buikvliesholte met verskeuring van die lewer en/of milt, en, eindelik, eienaardige veranderinge in die vel.

Uit die borsletsels kon die waarskynlike opvolging van die verwondinge op sy beste nagespeur word. Die longbeserings was erg. Makroskopies het die longmassa as gekneus, verskeur of selfs verbrysel vertoon; emfisemiese blasies was teenwoordig, en die oppervlaktes was bedek met bloedvlekkies onder die borsvlies. Mikroskopiese lugswellings, bloeding en stuwing is gevind. Die mees betekenisvolle bevindings was

lesions were severe. Macroscopically, the lung substance was contused, lacerated or actually pulped; emphysematous bullae were present and the surfaces were covered with subpleural petechiae. Microscopical emphysema, haemorrhage and congestion were found. The most significant findings, however, were the presence of fat emboli in the pulmonary vessels, the presence of moderate to severe collections of blood (0·3 to 2 litres) in the pleural spaces and the absence of any features to suggest drowning. From these findings some highly probable conslusions can be drawn. Firstly, since the fat emboli came obviously from the antemortem skull fractures, the occupants must have lived, or at least maintained a pulmonary circulation, for a sufficient interval to allow of the passage of the emboli from the base of the skull to the lungs *via* the heart. On the other hand, the absence of signs of drowning rules out the possibility of the occupants having lived for long; they were dead by the time that they reached the water.

The injuries can therefore be separated into 3 distinct groups; firstly, the head injury, followed in a moment or so by the *coup de grâce*—in all instances the pulmonary-thoracic disintegration—accompanied (or followed after death) by a train of bizarre injuries such as a fractured spine and limbs. Finally there were the skin injuries, which in the Elba accident were probably due to scalding under water by a subsequent kerosene fire on the surface, and in the Naples accident, were due to a phenomenon described by Meirowsky in 1909, namely post-mortem sun-tanning.

Having established the most feasible, and indeed reasonably probable, sequence of injuries, the medical team had next to investigate their causation. The head injury could be explained by violent displacement of the occupant at the moment of 'failure' so that the head struck the cabin ceiling with sufficient force to fracture the skull. However, controversy ranged around the chest injuries. It was known that a similar type of injury was encountered in exposure to blast, e.g. from gun fire or detonation of explosives, and it was believed that it might occur in sudden (explosive) decompression of the pressurized cabin of the *Comet* caused by structural failure. This, however, was ruled out by theoretical calculations and the most likely cause given is the expulsive effect of the large volume of air suddenly released when the pressure-cabin failed. The decompression injury which manifested itself in characteristic fashion as a thoracic-cage disintegration was complicated by the injuries sustained when the occupants struck the sea. A fall of 2,000 feet is adequate for the body to attain its terminal velocity of 160 feet per second. The post-mortem spine and limb fractures and perhaps some of the ruptured viscera, and the accumulation of blood in the body cavities, can be ascribed to this violence, but it is not possible to separate these injuries from those sustained at the moment of disintegration of the aircraft.

It seems clear from the investigations of the aeronautical experts that there was neither a fire in the cabins nor a bomb explosion, and that the essential egter die aanwesigheid van vetdruppels in die longbloedvate, die aanwesigheid van middelmatige tot groot versamelings bloed (0·3 tot 2 liter) in die borsvliesholtes, en die afwesigheid van enige tekens wat op verdrinking gedui het. Uit hierdie bevindings kan enkele hoogswaarskynlike gevolgtrekkinge gemaak word. Eerstens moes die insittendes nog lank genoeg geleef het, of minstens moes die bloedsomloop in die longe lank genoeg ononderbroke voortgegaan het om die vetdruppels, wat klaarblyklik van die voordoodse skedelbreuke afkomstig was, geleentheid te bied om die longe *via* die hart te bereik. Aan die ander kant bewys die feit dat daar geen tekens van verdrinking was nie dat die passasiers nie lank kon geleef het nie; hulle was dood toe hul die water bereik het.

Die beserings mag dus in 3 duidelik onderskeibare groepe verdeel word. Eerstens die kopbesering wat byna onmiddellik opgevolg is deur die *coup de grâce*—in alle gevalle die skeuring van die longe en borskas—vergesel van (of na die dood opgevolg deur) 'n reeks ongewone verwondinge soos die breek van die ruggraat en ledemate. Eindelik was daar die letsels van die vel. In die geval van die Elba-ongeluk is laasgenoemde waarskynlik veroorsaak deur brandwonde onder die water as gevolg van 'n latere keroseenvuur op die water. By Napels was hierdie letsels miskien te wyte aan nadoodse sonbrand, 'n verskynsel wat in 1909 deur Meirowsky beskryf is.

Nadat hulle die doenlikste en inderdaad die redelikste en waarskynlikste verloop van die beserings vasgestel het, moes die mediese span toe die oorsaak van hierdie beserings probeer vasstel. Die kopwonde kon verklaar word deurdat die passasiers hard genoeg uit hul sitplekke teen die plafon van die kajuit gewerp is om skedelbreuk te veroorsaak. Die borswonde was egter die strydvraag. Dit is welbekend dat soortgelyke wonde deur blootstelling aan ontploffing soos bv. dié van kanonvuur of die ontploffing van springstof veroorsaak word. Daar is dus gemeen dat hierdie beserings moontlik die gevolg was van die skielike (ontploffende) drukvermindering van die lugdrukgereelde kajuit van die *Comet*, veroorsaak deur 'n verswakking in die struktuur. Hierdie oorsaak is egter deur teoretiese berekeninge uitgeskakel, en as waarskynlikste is aangegee die uitwerpende krag van die groot hoeveelheid lug wat skielik losgelaat is toe die lugdrukgereelde kajuit ingegee het. Die besering weens drukvermindering wat homself op kenmerkende wyse as desintegrasie van die borskasholte openbaar het, is gekompliseer deur die beserings wat opgedoen is toe die insittendes die see-oppervlakte getref het. 'n Val van 2000 voet is genoeg vir die liggaam om 'n eindsnelheid van 160 voet per sekonde te bereik. Aan hierdie geweld kan die nadoodse rug- en ledemaatbreuke en miskien ook party van die ingewandskeurings toegeskryf word, asook die ophoping van bloed in die liggaamholtes, maar dit is nie moontlik om hierdie verwondinge te skei van die wat opgedoen is ten tyde van die verbrokkeling van die vliegtuig nie.

Uit die navorsing van die lugvaartkundiges skyn dit duidelik te wees dat daar geen brand in die kajuit, of 'n bomontploffing was nie, en dat die grondliggende

cause of the disasters was failure of the pressurized cabin. The Elba disaster was accompanied by a loud explosion, which can therefore be likened to that produced by the pricking of a balloon. The aviation-forensic medicine experts responsible for this investigation have enhanced the status of their science in the modern world by their investigations into these two disasters.

1. Armstrong, J. A., Fryer, D. I., Stewart, W. K. and Whittingdon, H. E. (1955): **1**, 1135.

oorsaak van die rampe gesoek moet word in die verbrokkeling van die lugdrukgereelde kajuit. Die Elba-ramp was vergesel van 'n harde ontploffing, wat dus vergelyk kan word met dié van die prik van 'n ballon. Die lugvaart-geregtelikmediese deskundiges wat vir hierdie ondersoek verantwoordelik was, het die status van hul wetenskap in die moderne wêreld met hul navorsings insake hierdie twee rampe aansienlik verhoog.

1. Armstrong, J. A., Fryer, D. I., Stewart, W. K. en Whittingdon, H. E. (1955): *Lancet*, **1**, 1135.

COMPLICATIONS WITH CHLORPROMAZINE

The increasing use of chlorpromazine (Largactil), particularly in the field of anaesthesia and psychiatric disturbance, has disclosed a number of pharmacological side-effects and toxic reactions. Originally Courvoisier *et al.* found the drug to be relatively non-toxic to laboratory animals, but its clinical use shows that it may be toxic to man.

We publish in this issue on page 677 an article by Drs. Bersohn and Wallace, of the South African Institute for Medical Research, on jaundice caused by chlorpromazine therapy, in which 5 cases of this condition are described and details are given of the laboratory findings. On page 673 we also publish an article by Dr. N. Shapiro, of Durban, recording a case in which agranulocytic angina developed suddenly after 11 weeks of treatment with chlorpromazine, and recovery ensued on discontinuance and treatment with penicillin and cortisone.

Recently Lomas *et al.*[1] reported on their findings with chlorpromazine in a series of 800 cases in a mental hospital. Mild hypotensive symptoms occurred in elderly or arteriosclerotic patients and initial tachycardia was invariably found to be present. There was a pronounced increase in appetite and weight, particularly in patients on a long course of treatment; and in this type of case it was observed as well that the more chronic the psychosis the less were the side-effects. Toxic reactions bore a relationship to the duration of treatment, but to little else; the size of dosage, the total dosage and the route of administration were unimportant. After the first week pyrexia was the commonest complication; at the end of the second, skin reactions and jaundice occurred and, a little later on, alteration in the blood picture. The skin reactions, either an erythema on the exposed parts or else a morbilliform rash which cleared up irrespective of whether the drug was continued or not, were commonest in elderly females. The jaundice, which is a manifestation of a toxic hepatitis, may be fatal, especially if there is a previous history of liver damage, which should therefore be an absolute contra-indication to chlorpromazine.

After the first month complicating blood dyscrasias should be anticipated. Lomas and his co-workers performed weekly blood-counts on a group of the 800 patients and found that in the majority the erythrocyte sedimentation rate rose to a maximum after a month and then declined slowly. In some a leucopenia developed in the 4th week, which cleared up when the drug was withheld. In the one case of agrunulocytosis encountered, the white-cell count rapidly reverted to normal level when treatment was stopped.

Summing up, then, it seems that the principal safeguards to be taken in chlorpromazine therapy are (1) to confine elderly or arteriosclerotic subjects to bed in order to combat the hypotension, (2) to withdraw the drug completely on the appearance of jaundice (and to use it not at all where a previous history of liver damage exists), and (3) to be ever vigilant for a change in the blood picture. The safest course is probably to perform weekly blood-counts throughout the time that chlorpromazine is given.

1. Lomas, J., Boardman, R. H. and Markowe, M. (1955): *Lancet*, **1**, 1144.

CHLORPROMAZINE (LARGACTIL) JAUNDICE

I. BERSOHN, B.SC., M.B., B.CH. and B. V. WALLACE, B.SC., M.B., B.CH.

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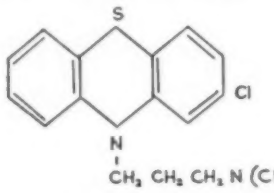
Chlorpromazine hydrochloride (Largactil) is a phenothiazine derivative, the discovery of which resulted when workers in the Rhône-Poulenc-Spécia Laboratories in France were looking for a substitute for promethazine which, while simulating promethazine, would have a more marked central depressant action. Chlorpromazine hydrochloride is 3-chloro-10 (3[1]—dimethylamino—*n*—propyl) phenothiazine hydrochloride and has the structure shown in illustration on page 678. It is, therefore, chemically related to promethazine hydrochloride (Phenergan) and diethazine hydrochloride (Diparcol), which are antihistaminic drugs.

The drug, which can be administered either orally or by intramuscular or intravenous injection, has been found to be of definite value in a large variety of conditions. Amongst some of the clinical states which respond favourably to it are nausea and vomiting, including the vomiting of pregnancy, uraemia, labyrinthitis, radiation sickness, the vomiting accompanying advanced malignant disease, and the nausea often associated with drugs such as morphine and codeine. It has been used in the relief of pain and, when administered with recognized analgesics, enhances the effects of the latter. Pruritic conditions, including the pruritus so often associated with obstructive jaundice, eczema and cases of chronic urticaria and dermatitis herpetiformis, respond favourably to chlorpromazine hydrochloride.



Molecular Weight 355·3 Melting Point ± 195°C

The drug has been used as a hypothermic agent in cases of hyperpyrexia where reduction in temperature is essential. In the field of psychiatry chlorpromazine hydrochloride has been used as a sedative in severe agitation and in states of moderate restlessness. Acute psychotics, neurotics and psychoneurotics requiring sedatives react well to the drug, and it has been found most useful in postlobotomy, delirium tremens, acute alcoholism and intractable insomnia, and in the treatment of symptoms arising from sudden withdrawal of narcotic drugs.

In anaesthesia, the drug has been used in pre-anaesthetic medication either local or general and prior to instrumentation, and has been found to enhance or facilitate anaesthesia.

Amongst some of the side effects produced by the drug in man are: (1) hypotension, (2) hypothermia, (3) polyuria, (4) constipation, (5) drowsiness, (6) motor retardation with an unsteady gait, (7) weakness and tiredness, (8) dryness of the mouth and upper respiratory passages, especially at night, and (9) a characteristic pallor of the skin.

Recently, in the medical literature, there have appeared several reports of the development of jaundice due to chlorpromazine hydrochloride:

Zatuchni and Miller[1] report in detail one case of jaundice, which was diagnosed as being due, probably, to a carcinoma of the pancreas. The patient was subjected to laparotomy with negative results, and was eventually diagnosed as intra-hepatic obstructive jaundice. The jaundice appeared on the 14th day of chlorpromazine-hydrochloride therapy. Liver biopsy showed the portal tracts to be infiltrated with neutrophiles, eosinophiles, lymphocytes and large mononuclear cells, which extended into the adjacent hepatic parenchyma; some periportal hepatic cells were degenerated and others were undergoing phagocytosis; a few canaliculi were plugged with bile. These biopsy findings were consistent with an acute cholangio-hepatitis.

Winkelman[2] treated 142 neuropsychiatric patients with chlorpromazine hydrochloride, 3 of whom developed jaundice 2-5 weeks later. A liver biopsy on one of these cases showed chronic liver damage, and the authors suggested that jaundice might be precipitated by the drug in patients with impaired hepatic function.

Lehmann and Hanrahan[3] treated 71 psychiatric patients, 3 of whom developed jaundice, which appeared to be toxic in origin. The cephalin-cholesterol flocculation test was negative after 2-3 weeks.

Garmany, May and Folkson[4] treated 29 psychoneurotics with chlorpromazine hydrochloride, 25 mg. *t.d.s.* orally, increased by 25 mg. every other day to a maximum of 75 mg. *t.d.s.* Three cases developed pyrexia (101-103°F) with epigastric and right subcostal tenderness. Three other cases showed bilirubinuria and abnormal bromsulphalein dye retention with normal flocculation tests.

Azima and Ogle[5] observed jaundice in 5 out of 100 patients under chlorpromazine-hydrochloride therapy. The jaundice was obstructive in type as assessed by clinical and laboratory means. These authors suggest that chlorpromazine hydrochloride may sensitize the liver to further attack by viral or toxic agents, but make mention that their jaundiced cases appeared during a mild epidemic of hepatitis.

Moyer *et al.*[6] observed a single case of jaundice amongst 500 patients treated with the drug. This patient received 50 mg. of chlorpromazine hydrochloride 4 times a day for 2 weeks.

Van Ommen and Brown[7] report on 3 cases of jaundice due to the drug. One of these cases developed jaundice 2 weeks after administration of chlorpromazine hydrochloride, 25 mg. *t.d.s.* Laboratory tests were indicative of an obstructive type of jaundice. Surgical exploration revealed no evidence of extra-hepatic obstruction and a liver biopsy showed marked bile stasis with phagocytosis of bile pigment by the Kupfer cells. The second case developed jaundice after cessation of the drug, which the patient had taken for 19 days (50 mg. *t.d.s.*). The third case developed jaundice following chlorpromazine-hydrochloride therapy given after labyrinthotomy. One of these cases showed an eosinophilia, and the alkaline phosphatase was moderately elevated in one case only.

Considering the number of clinical conditions where chlorpromazine hydrochloride is being used, the number of reported cases of jaundice attributed to the drug indicates a low incidence of this complication. Examination of the literature reveals some 257 cases treated with chlorpromazine hydrochloride, no mention being made that any of them developed jaundice.[8-13]

However, although jaundice appears to be a rare sequel of the administration of chlorpromazine hydrochloride (Largactil), 5 cases of jaundice followingtreatment with this drug have recently been investigated by us.

CASE REPORTS

Case 1. Dr. Z, a female practitioner aged 29 years, and 3 months pregnant, was treated with Largactil, 25 mg. daily, because of morning sickness, for approximately 3 weeks. This patient had never been jaundiced previously and apart from childhood illnesses and an attack of atypical pneumonia, the past history showed nothing of significance. The patient stated that her family was an 'allergic' one.

After approximately 3 weeks of Largactil therapy, she developed jaundice and the drug was stopped. Ten days before the development of the jaundice, she had a slight temperature (101°F) for about 48 hours, complaining of pain in all her joints, marked anorexia, vomiting, slight epigastric discomfort, constipation and rigors.

Approximately a week after this episode, severe and distressing pruritus developed, most marked in the palms of the hand and the soles of the feet. The patient became jaundiced 48 hours later, her stools being pale and her urine dark. The pruritus was the most unpleasant symptom of the condition and lasted as long as the clinical jaundice. Three weeks after jaundice developed the liver was enlarged 1½ inches below the costal margin. The entire episode lasted approximately 6 weeks, the patient making an uneventful recovery.

The total dosage of Largactil was approximately 25×25 mg. tablets.

The laboratory findings in this case are given in Table I.

Case 2. Mrs. M, a housewife aged 58 years, was advised by a lay person to take Largactil tablets because she was feeling depressed and lacked energy. The patient had never been jaundiced previously. She had a history of dyspepsia at irregular intervals for the past 10 years, 5 years previously she had pneumonia, and a year later she suffered from angioneurotic oedema of the face, and urticaria, which lasted 6 weeks. Six months before taking Largactil she had penicillin injections for influenza.

The patient took 42 tablets in one week. A few days later she noticed that her urine was becoming darker, experienced abdominal discomfort and pain, and developed diarrhoea. Ten days later, this was followed by a sudden attack of nausea, vomiting, fever and rigors and the patient fainted. The abdominal pain and discomfort in the meantime passed off, but the patient noticed increasing yellowness of the eyes and skin, she passed clay-coloured stools, and she suffered severely from pruritus of the hands and feet. On physical examination, the liver edge was not palpable but there was diminished dullness of the liver to percussion.

The total dosage of Largactil was 42×25-mg. tablets.

The laboratory findings in this case are given in Table II.

Case 3. Mrs. G, a housewife aged 37 years, was admitted to Johannesburg General Hospital on 31 December 1954 with polyarthritis of the hands, erythema multiforme, sore throat, and fever. She had been treated with sulphonamides, terramycin, salicylates and cortisone before her admission. At no time in the past had the patient been jaundiced. Whilst in hospital she was treated with crysticillin, cortisone, ACTH and digitalis.

As she was highly excitable, Largactil therapy (25 mg. *t.d.s.*) was given. The drug was stopped 21 days later because the patient became jaundiced, with clay-coloured stools and dark urine. Her main complaint throughout the period of jaundice was of severe pruritus. She was still slightly jaundiced 8 weeks after the first appearance of jaundice.

The total dosage of Largactil was 63×25-mg. tablets.

Table III summarizes the biochemical tests done on this patient, including biochemical investigations before the onset of jaundice.

Case 4. Mrs. L, a housewife aged 55, was admitted to the Johannesburg General Hospital on 13 February 1955. A few days before her admission she had fever (102°F), pain in the thighs, vomiting of bile-like material, and pain in the epigastrium, which was continuous and stabbing. She had undergone cholecystectomy, appendicectomy and hysterectomy for fibroids 30, 7 and 3 years ago respectively. She had 18 months previously complained of a pain in the left iliac fossa and diarrhoea, which lasted for 2 months. The patient had never been jaundiced but stated that she had been in contact with a case of jaundice 3 weeks before admission. The history as given by the patient was very unreliable, but 11 days before her admission to hospital she attended the out-patient department of the hospital, where Lumina and Largactil tablets were prescribed. She stated that she only took one of these tablets, felt ill and did not continue. About a week later the out-patient records show that she again attended the department and was given Largactil tablets, suggesting that she had taken those issued on the first occasion.

Eleven days after her admission to the hospital she was, owing to her excitability, given Largactil, 25 mg. *b.d.*, intramuscularly for 3 days (24-27 February). There was a very slight degree of jaundice at the time of admission, which increased in severity during her stay in hospital, and a diagnosis was made of carcinoma of the head of the pancreas. Laparotomy revealed no evidence of malignancy nor extra-hepatic obstruction. A liver biopsy was not done.

The laboratory findings in this case are given in Table IV.

Case 5. Mrs. C, aged 73 years, was admitted to the hospital with pain in the epigastrium and in the left and right iliac fossae and a history of vomiting, anorexia and nausea for about 1 day with a pyrexia of 100°F. The patient was slightly jaundiced. There was a history of 7½-lb. loss in weight. She had many years ago undergone cholecystectomy, appendicectomy and a tubal pregnancy. At no time in the past had she been jaundiced.

The patient had consulted various doctors for dyspepsia and constipation and had been labelled as a case of anxiety neurosis. For this she was given 25 mg. Largactil *t.d.s.*. After taking the tablets for 9 days she noticed that she was becoming jaundiced. Her condition was diagnosed clinically as being due to an ampullary carcinoma of the head of the pancreas or a primary carcinoma in the gut with secondaries in the porta hepatis.

On examination, her abdomen was somewhat distended. No masses were palpable, but the patient was difficult to examine owing to tensing of her muscles. X-ray examinations of the gastro-intestinal and biliary tracts did not reveal any evidence of malignancy. The jaundice gradually improved and approximately 7 weeks after her admission she was discharged as 'clinically normal'.

The total dosage of Largactil was 27×25-mg. tablets.

The laboratory findings in this case are given in Table V.

ANALYSIS OF LABORATORY FINDINGS

One of the main reasons for performing 'liver function tests' in a jaundiced patient is to attempt to differentiate between parenchymal or medical jaundice and extra-hepatic obstructive or surgical jaundice. Where only a few selected liver tests are done, one usually relies on the thymol turbidity and flocculation test, the cephalin-cholesterol flocculation, the colloidal-red test, the alkaline phosphatase level, protein fractionation including gamma globulin, and cholinesterase and cholesterol estimations, including the ratio of esterified to total cholesterol. More recently another estimation has been added to the list, the serum-mucoprotein content. In obstructive jaundice, generally speaking, flocculation tests are normal, protein fractions including gamma globulin show no gross departures from normal values, the percentage of esterified cholesterol is within normal limits and the mucoprotein level is raised. Greenspan and Dreiling[14] show that a reduction of serum-mucoprotein occurs in 80% of parenchymal liver disease and that in inflammatory or neoplastic obstructive biliary-tract disease, especially when the

condition has lasted for some time, mucoprotein is increased.

In differentiating between medical and surgical jaundice, the blood count may be of value, particularly the leucocyte count, which usually shows a neutrophilia in surgical jaundice and is normal or decreased in medical jaundice. The sedimantation rate, when normal, favours a diagnosis of medical jaundice, but a raised sedimentation rate, whilst not excluding primary liver disease, is always found in post-hepatic obstructive jaundice.

In the cases reported, the flocculation tests were negative throughout the course of the illness, with the exception of case 3, which, before Largactil was given, showed a slightly elevated thymol turbidity on one occasion, with a doubtful thymol flocculation, which tests subsequently became normal. The alkaline phosphatase in all cases was elevated, which placed the jaundice in the extra-hepatic group.

There were no gross disturbances in the albumin-globulin ratio, nor was the gamma-globulin content of the serum significantly altered. The pseudo-cholinesterase values all fell within the range of normality.

The ratio of esterified cholesterol to total cholesterol was normal (except on one occasion in case 3) but a significant feature was the elevated cholesterol and lipid content of the serum, especially in cases 2 and 3. The mucoprotein (normal range 50-110 mg.%, mean 80 mg.%) was essentially within normal limits in cases 1 and 2 but was high in case 3. Case 3, however, it will be recalled, was admitted to the hospital for an undiagnosed febrile disease and, with the appearance of jaundice, the figure for the mucoprotein fell. In case 4 the mucoprotein level was within normal limits and mucoprotein estimations were not done in case 5.

The blood count showed no significant changes in the haemoglobin, red-cell and leucocyte counts, but cases 1, 2, 3 and 4 showed an eosinophilia. An elevated sedimentation rate was present in all cases and remained high, despite a decrease in the bilirubin level towards the end of the episodes.

The prothrombin index was normal in all cases.

Thus all cases investigated, from a laboratory point of view, fell into the category of an obstructive type of jaundice. The course of the disease, especially when liver biopsies carried out by other workers are taken into consideration, suggests an intra-hepatic type of obstructive jaundice. The only laboratory features which were not in keeping with a diagnosis of surgical extra-hepatic jaundice were the eosinophilia and the normal mucoprotein level.

DISCUSSION

'Intra-hepatic obstructive jaundice' can be defined as jaundice in which no evidence of extra-hepatic obstruction can be demonstrated, and in which the laboratory findings are similar to those found in surgical jaundice. It is vital that the existence of this 'non-surgical type of simulated surgical jaundice' be recognized, or otherwise patients may be subjected to unnecessary operative interference. This phase of intra-hepatic obstructive jaundice occurs even in cases of viral hepatitis, but usually for a short period, though occasionally it may last for weeks.

Certain drugs such as arsphenamine, thiouracil and methyl testosterone are known to have produced 'intra-hepatic obstructive jaundice'. Hanger and Gutman[15] described 12 such cases due to arsphenamine. Biochemical tests suggested surgical jaundice, but liver biopsy showed a cholangitis and pericholangitis, bile plugs in the bile capillaries, and no significant involvement of liver cells. The jaundice was attributed to inflammatory changes about the bile passages and to bile thrombi within the canaliculi. The selective involvement of the finer biliary radicles was thought to be due to a toxic reaction induced in predisposed individuals by the drug in an altered form.

Gargill and Lesses[16] reported 2 cases of intra-hepatic obstructive jaundice due to thiouracil, with laboratory features of an extra-hepatic lesion. A laparotomy performed on one case showed no evidence of such obstruction, while liver biopsy revealed normal liver tissue, intracanalicular bile thrombi and periportal round-cell infiltration.

Werner, Hanger and Kritzler[17] described 7 cases of jaundice following methyl testosterone therapy which simulated, biochemically, regurgitation jaundice. Liver biopsies in 2 cases showed bile stasis and plugging of the bile canaliculi in the central zone of the lobule, but no lesions in the portal triads.

In our series no liver biopsies were carried out. From clinical and laboratory data, it is our opinion that the basic etiological factor in chlorpromazine jaundice is allergic. Four of our 5 cases showed an eosinophilia, and there was an allergic history, either personal or familial, in cases 1 and 2. Other evidence in favour of allergy is that skin sensitization amongst hospital staff handling the drug has been reported, as well as skin rashes and arthralgias in cases receiving therapy. In one case,[18] not in our series, the effect of hydrocortone was tried, on the assumption that the jaundice was allergic in origin. There was a prompt drop in the eosinophilia and the bilirubinaemia rapidly returned to normal. Hanger and Gutman[15] stated that their cases had the characteristics of a drug hypersensitivity, whilst Werner *et al.*[16] postulated that methyl testosterone caused injury to the liver cells, producing a disturbance of the normal hydration of the bile, which then became too viscous to flow through the interlobular system.

Zatuchni and Miller[1] favoured a hypersensitivity in their case of chlorpromazine jaundice. We feel that the jaundice produced in our cases can be explained on an allergic basis. Oedema of the liver cells (as evidenced clinically by liver enlargement) ensues as a result of an allergic response to the drug, and this produces a narrowing of the bile canaliculi, bile stasis with formation of bile thrombi, and intra-hepatic obstruction. Alternate mechanisms on an allergic basis may be spasm of the bile canaliculi similar to bronchiolar spasm in asthma, tending to produce an intra-hepatic obstructive lesion, or oedema of the walls of the bile canaliculi, which may alter the osmotic pressure of the bile, with consequent stasis, formation of bile thrombi, and jaundice.

SUMMARY

1. Five cases of intra-hepatic obstructive jaundice due to Largactil (chlorpromazine hydrochloride) are described.

2. Laboratory findings suggest an extra-hepatic obstructive type of jaundice.

3. Possible mechanisms causing the jaundice are discussed.

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ADDENDUM

Since writing this paper we have investigated 4 further cases of Largactil jaundice. Each of these cases gave laboratory findings suggestive of obstructive jaundice, an eosinophilia and a normal mucoprotein level.

All 4 patients made uneventful recoveries.

TABLE I. LABORATORY FINDINGS IN CASE 1 (DR. Z), 1954-55

	17 *December*	20 *December*	29 *December*	6 *January*	19 *January*	24 *February*
Thymol Turbidity (Units)	1·5	2·0	1·5	1·0	2·0	1·5
Thymol. Flocculation	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
Colloidal-red Flocculation	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
Cephalin Cholesterol Flocculation	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
Takata-Ara Reaction	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
Zinc Sulphide Reaction (Units)	14·0	18·6	16·8	17·8	15·0	12·4
Total Lipid (Künkel) (mg.%)	576	640	491	551	660	755
Alkaline Phosphatase (King-Armstrong Units)	40·4	38·9	24·9	24·2	23·2	7·7
Van den Bergh	Weak Prompt Direct	Prompt Direct	Prompt Direct	Prompt Direct	Prompt Direct	Neg.
Direct Bilirubin (mg.%)	1·5	3·9	2·8	2·5	2.0	0·1
Total Bilirubin (mg.%)	2·2	5·2	4·5	3·3	3·0	0·3
Albumin (mg.%)	3·7	3·8	3·2	3·3	3·5	4·0
Globulin (g.%)	3·4	4·0	4·3	3·7	3·6	2·8
Gamma Globulin (g.%)	1·27	1·15	1·21	1·61	1·41	1·15
Pseudo-cholinesterase (% Normal)	93	87	81	96	100	100
Mucoprotein (mg.%)	—	86	89	113	90	89
Polysaccharide (mg.%)	—	16	17	22	16	13
P/M Ratio	—	0·18	0·19	0·19	0·17	0·14
Total Cholesterol (mg.%)	—	333	205	218	—	307
Free Cholesterol (mg.%)	—	108	64	63	—	71
Cholesterol Esters	—	225	141	155	—	236
% Esters to Total	—	67	69	71	—	77
Erythrocytes (Millions per c.mm.)	—	4·87	4·22	4·40	4·40	4·40
Haemoglobin (g.%)	—	14·2	12·5	12·7	12·6	12·8
Leucocytes (per c.mm.)	—	8,800	11,300	7,300	5,800	9,400
Neuthrophiles (%)	—	52	68	69	53	57
Mononuclears (%)	—	5·5	8	3·5	3·0	4·0
Lymphocytes (%)	—	33·5	19	20·5	40·0	35·5
Eosinophiles (%)	—	9·0	5	7·0	4·0	3·5
Sedimentation Rate (Wintrobe) (mm. in 1 hour)	—	35	49	52	53	47
Packed Cell Volume (%)	—	43	38	39·5	—	38
Prothrombin Index (% Normal)	—	85	90	85	93	88
Bilirubinuria	—	—	4+	4+	—	Absent
Urobilinuria	—	—	3+	4+	—	2+

TABLE II. LABORATORY FINDINGS IN CASE 2 (MRS. M), 1955

	15 *February*	23 *February*	9 *March*	16 *March*	28 *March*
Thymol Turbidity (Units)	3·5	3·5	3·5	1·5	2·5
Thymol Flocculation	Neg.	Neg.	Neg.	Neg.	Neg.
Colloidal-red Flocculation	1+	Neg.	Neg.	Neg.	Neg.
Cephalin Cholesterol Flocculation	Neg.	Neg.	Neg.	Neg.	Neg.
Takata-Ara Reaction	Neg.	Neg.	Neg.	Neg.	Neg.
Zinc Sulphate Turbidity (Units)	7·4	10·6	8·2	7·4	9·0
Total Lipid (Künkel) (mg.%)	1,930	2,557	1,014	660	660
Alkaline Phosphatase (King-Armstrong Units)	48·5	44·4	14·7	15·3	14·5
Van den Bergh	Prompt Direct	Prompt Direct	Prompt Direct	Prompt Direct	Delayed Direct
Direct Bilirubin (mg.%)	11·8	9·6	2·0	2·1	0·8
Total Bilirubin (mg.%)	16·8	13·8	2·8	2·5	1·0
Albumin (g.%)	3·7	3·6	3·4	4·0	3·8
Globulin (g.%)	4·1	3·8	3·4	3·3	3·5
Gamma Globulin (g.%)	1·47	1·47	0·78	0·78	1·02
Pseudo-cholinesterase (% Normal)	100	100	93	100	100
Mucoprotein (mg.%)	114	98	76	77	76
Polysaccharide (mg.%)	19	15	15	16	15
P/M Ratio	0·16	0·15	0·19	0·20	0·19
Total Cholesterol (mg.%)	595	—	481	356	286
Free Cholesterol (mg.%)	250	—	134	98	70
Cholesterol Esters (mg.%)	345	—	347	258	216
% Esters to Total	58	—	71	72	75
Erythrocytes (millions per c.mm.)	5·80	4·91	4·93	5·22	4·79
Haemoglobin (g.%)	17·5	14·7	14·4	15·2	14·8
Leucocytes (per c.mm.)	7,500	7,400	8,200	6,200	8,700
Neutrophiles (%)	36·0	34·0	47·5	27·0	28·0
Mononuclears (%)	5·5	5·5	5·5	7·0	4·0
Lymphocytes (%)	46·5	52	33·5	57·5	68·0
Eosinophiles (%)	12·0	8·0	13·5	8·0	0
Sedimentation Rate (Wintrobe) (mm. in 1 hour)	8·0	32	27	25	25
Packed Cell Volume (%)	51	45	43	45	44·5
Prothrombin Index (% Normal)	90	93	98	87	82·1
Bilirubinuria	4+	4+	—	Absent	Absent
Urobilinuria	4+	4+	—	1+	3+

TABLE III. LABORATORY FINDINGS IN CASE 3 (MRS. G), 1955

	4 *January*	21 *January*	25 *January*	2 *February*	23 *February*	15 *March*
Thymol Turbidity (Units)	3·0	—	5·0	4·5	4·0	4·0
Thymol Flocculation	Doubtful	—	Neg.	Neg.	Neg.	Neg.
Colloidal-Red Flocculation	1+	—	1+	Neg.	Neg.	Neg.
Cephalin Cholesterol Flocculation	Neg.	—	Neg.	Neg.	Neg.	3+
Takata—Ara Reaction	Neg.	—	Neg.	Neg.	Neg.	Neg.
Zinc Sulphate Turbidity (Units)	13·2	—	6·6	6·6	4·2	7·4
Total Lipid (Künkel) (mg.%)	471	—	875	2,278	4,581	2,796
Alkaline Phosphatase (King-Armstrong Units)	7·1	—	21·6	46·0	24·2	16·5
Van den Bergh	Indirect	—	Prompt Direct	Prompt Direct	Prompt Direct	Weak Prompt Direct
Direct Bilirubin (mg.%)	0·4	—	2·5	13·1	7·8	1·5
Total Bilirubin (mg.%)	0·7	—	3·7	17·3	12·2	2·3
Albumin (g.%)	3·2	—	3·3	2·9	2·7	3·6
Globulin (g.%)	3·5	—	2·8	3·0	2·9	2·3
Gamma Globulin (g.%)	1·08	—	0·96	1·47	1.34	1·15
Pseudo-cholinesterase (% Normal)	69	—	89	100	83	81
Mucoprotein (mg.%)	290	—	—	186	124	146
Polysaccharide (mg.%)	—	—	—	—	20	25
P/M Ratio	—	—	—	—	0·13	0·17
Total Cholesterol (mg.%)	—	—	—	—	801	976
Free Cholesterol (mg.%)	—	—	—	—	246	500
Cholesterol Esters (mg.%)	—	—	—	—	555	476
% Esters to Total	—	—	—	—	69	49
Erythrocytes (millions per c.mm.)	5·04	—	—	—	—	4·68
Haemoglobin (g.%)	14·6	15·4	14·4	14·5	—	13·8
Leucocytes (per c.mm.)	11,100	7,100	10,200	9,500	—	11,700
Neutrophiles (%)	—	74	64	63·5	—	63·5
Mononuclears (%)	—	4·0	4·0	5·5	—	5·0
Lymphocytes (%)	—	14·0	28	29·5	—	30·5
Eosinophiles (%)	—	8·0	4	1·5	—	0·5
Sedimentation Rate (Wintrobe) (mm. in 1 hour)	23	—	30	—	—	42
Packed Cell Volume (%)	—	—	44	—	—	42
Prothrombin Index (% Normal)	89	—	—	49	—	94

TABLE IV. LABORATORY FINDINGS IN CASE 4 (MRS. L), 1955

	14 *February*	25 *February*	1 *March*	8 *March*	18 *March*
Thymol Turbidity (Units)	1·0	—	1·0	—	1·0
Thymol Flocculation	Neg.	—	Neg.	—	Neg.
Colloidal-Red Flocculation	Neg.	—	Neg.	—	Neg.
Cephalin Cholesterol Flocculation	Neg.	—	Neg.	—	Neg.
Takata-Ara Reaction	Neg.	—	Neg.	—	Neg.
Zinc Sulphate Reaction (Units)	4·2	—	13·2	—	12·4
Total Lipid (Künkel) (mg.%)	411	—	531	—	805
Alkaline Phosphatase (King-Armstrong Units)	15·4	—	26·4	—	26·2
Van den Bergh	Delayed Direct	—	Prompt Direct	—	Prompt Direct
Direct Bilirubin (mg.%)	0·7	—	4·4	—	6·6
Total Bilirubin (mg.%)	1·3	—	6·0	—	9·6
Albumin (g.%)	3·4	—	3·9	—	3·0
Globulin (g.%)	3·3	—	3·6	—	3·4
Gamma Globulin (g.%)	0·96	—	1·15	—	0·96
Pseudo-chonnesterase (% Normal)	100	—	100	—	95
Mucoproteili (mg.%)	—	—	—	66	—
Polysaccharide (mg.%)	—	—	—	—	—
P/M Ratio	—	—	—	—	—
Total Cholesterol (mg.%)	—	—	—	—	—
Free Cholesterol (mg.%)	—	—	—	—	—
Cholesterol Esters	—	—	—	—	—
% Esters to Total	—	—	—	—	—
Erythrocytes (millions per c.mm.)	—	—	—	—	—
Haemoglobin (g.%)	14·5	16·3	15·3	—	—
Leucocytes (per c.mm.)	5,300	4,000	4,500	—	—
Neutrophiles (%)	55·5	62	43	—	—
Mononuclears (%)	3·5	5	3	—	—
Lymphocytes (%)	32·5	31	46	—	—
Eosinophiles (%)	8·0	1	6	—	—
Sedimentation Rate (Wintrobe) (mm. in 1 hour)	41	29	29	—	—
Packed Cell Volume (%)	40·0	45·5	44	—	—
Prothrombin Index (% Normal)	—	89	—	—	—
Bilirubinuria	—	—	—	—	—
Urobilinuria	—	—	—	—	—

TABLE V. LABORATORY FINDINGS IN CASE 5 (MRS. C), 1954-55

	29 *Nov.*	15 *Dec.*	24 *Dec.*	4 *Jan.*	12 *Jan.*	13 *Jan.*	20 *Jan.*	28 *Jan.*	8 *Feb.*	15 *Feb.*
Thymol Turbidity (Units)	—	—	1·0	1·0	1·0	—	1·0	4·0	2·0	1·5
Thymol Flocculation	—	—	Neg.	Neg.	Neg.	—	Neg.	Neg.	Neg.	Neg.
Colloidal-Red Flocculation	—	—	Neg.	Neg.	Neg.	—	Neg.	Neg.	Neg.	Neg.
Cephalin Cholesterol Flocculation	—	—	Neg.	Neg.	Neg.	—	Neg.	Neg.	Neg.	Neg.
Takata-Ara Reaction	—	—	Neg.	Neg.	Neg.	—	Neg.	Neg.	Neg.	Neg.
Zinc Sulphate Reaction (Units)	—	—	9·8	15·8	9·8	—	11·4	7·4	9·8	7·4
Total Lipid (Künkel) (mg.%)	—	—	551	830	730	—	596	730	640	531
Alkaline Phosphatase (King-Armstrong Units)	—	—	34·4	33·1	21·8	—	18	6·2	14·3	3·0
Van den Bergh	—	—	Prompt Direct	Prompt Direct	Delayed Direct	—	Weak Prompt Direct	Weak Prompt Direct	Delayed Direct	Neg.
Direct Bilirubin (mg.%)	—	—	3·2	2·7	1·7	—	1·2	1·3	1·0	0·1
Total Bilirubin (mg.%)	—	—	5·0	3·7	2·3	—	2·5	2·2	1·3	0·3
Albumin (g.%)	—	—	2·9	3·2	3·5	—	3·1	3·5	3·6	3·7
Globulin (g.%)	—	—	3·2	4·0	3·0	—	3·2	3·3	2·3	2·9
Gamma Globulin (g.%)	—	—	0·96	1·21	1·02	—	0·96	1·15	0·78	0·90
Pseudo-cholinesterase (% Normal)	—	—	87	70	80	—	66	100	80	72
Mucoprotein (mg.%)	—	—	—	—	—	—	—	—	—	—
Polysaccharide (mg.%)	—	—	—	—	—	—	—	—	—	—
P/M Ratio	—	—	—	—	—	—	—	—	—	—
Total Cholesterol (mg.%)	—	—	—	—	—	—	—	—	—	—
Free Cholesterol (mg.%)	—	—	—	—	—	—	—	—	—	—
Cholesterol Esters	—	—	—	—	—	—	—	—	—	—
% Esters to Total	—	—	—	—	—	—	—	—	—	—
Erythrocytes (millions per c.mm.)	—	—	—	—	—	—	—	—	—	—
Haemoglobin (g.%)	13·5	15·3	—	—	—	13·4	—	—	—	12·0
Leucocytes (per c.mm.)	7,600	6,500	—	—	—	7,200	—	—	—	5,900
Neutrophiles (%)	—	69·0	—	—	—	63	—	—	—	71·5
Mononuclears (%)	—	3·0	—	—	—	4·5	—	—	—	6·5
Lymphocytes (%)	—	24·0	—	—	—	31	—	—	—	21·5
Eosinophiles (%)	—	3·5	—	—	—	1·0	—	—	—	0·5
Sedimentation Rate (Wintrobe) (mm. in 1 hour)	33	22	—	—	—	34	—	—	—	37
Packed Cell Volume (%)	40	44	—	—	—	42	—	—	—	38
Prothrombin Index (% Normal)	—	—	—	—	—	100	—	—	—	—
Bilirubinuria	—	—	—	—	—	—	—	—	—	—
Urobilinuria	—	—	—	—	—	—	—	—	—	—

CONGENITAL TOXOPLASMOSIS IN SOUTH AFRICA

A REVIEW AND CASE REPORT

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Toxoplasmosis is a disease of world-wide distribution. *Toxoplasma gondii* is an intracellular protozoon parasite which infests a wide variety of hosts from birds and beasts through to man. In the past decade much interest has been shown in the parasite, but little is known about its biology or its epidemiology, particularly with regard to human infection.

Toxoplasmosis in symptomless. Benign or quiescent forms may occur at any age, but most recognized cases have been in infants exhibiting congenital abnormalities. The classical signs are hydrocephalus or microcephaly, chorioretinitis and cerebral calcification. Only rarely have the parasites been recovered from patients during life, and histological sections are only obtained at autopsy, when the diagnosis is sometimes established for the first time.

The first human case described in Africa was in the Congo and recorded by Wiktor[1] in 1950. In 1951 Jeliffe[2] reported a case in Western Nigeria. Since then 2 cases have been recorded from the Union of South Africa, as well as one from the Belgian Congo and one from Northern Rhodesia: In Cape Town Klenerman[3] described a fatal case of the congenital variety occurring in an African baby only a few weeks old and diagnosed *post mortem*, and Rabkin and Javett[4] diagnosed a case of the congenital type in a 4-year-old child from the Belgian Congo, who had apparently always been retarded. Becker[5] described 2 cases diagnosed *post mortem*. The one was a hydrocephalic infant aged 5 months who was born in Northern Rhodesia and died of meningitis on the Witwatersrand. The other was a 4½-year-old European child living on the Witwatersrand who had been ill for several weeks and who presented a terminal picture of encephalitis with coma and increased intracranial pressure.

The subject of this communication is believed to be the first reported case in an individual born in the Union of South Africa where the diagnosis was made during the lifetime of the patient, and it points to the existence of other cases in South Africa which must surely have passed unrecognized.

CASE REPORT

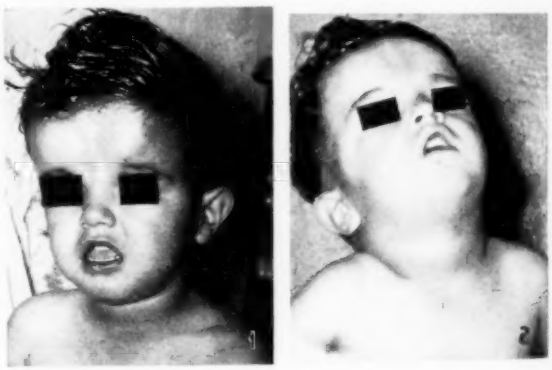
An Indian male child, about 15 months old, was first seen on 17 March 1953. The mother, aged 24 years, had been born in India, had resided in South Africa since the age of 9 years, and was then living at Rustenburg, Transvaal. One month before her confinement she came to Pretoria, where the baby was born. During pregnancy she had no obvious acute illness. She is married to a first cousin, and had lost 4 previous children, one aged 5 months, one at the age of 2 weeks, and twins aged only a few weeks. She has 2 surviving children, now aged 7 years and 4 years and since the birth of the child which is the subject of the present report had had another child which is now surviving and aged 14 months.

At home the parents keep fowls, some of which from time to time become ill. There are no animals or pets kept about the house, but cats or dogs from the neighbourhood occasionally stray into the backyard. The father is employed in a general dealer's store. The family have never eaten hares or other wild animals.

The mother was worried about the size of the child's head, and said that he was unable to keep it erect. The confinement had been a normal one, and the child was stated to have cried immediately upon being born, but the anterior fontanelle was apparently abnormally large.

On examination the patient did not appear acutely ill, but his appearance was that of a retarded child. His skull was dome-shaped with a bulging forehead; the circumference was 18 inches. The anterior fontanelle was not closed and measured 2¾×1¾ inches; it was not under tension and pulsated slightly. The metopic suture was still palpable. On the Gesell scale his developmental quotient was abnormally low. He was unable to sit and definitely did not have good control over the neck muscles. The reflexes were hyperactive, but no spasticity was noted. At the time he had otorrhoea of the left ear, which was treated with terramycin (see below). At this stage the child was lost sight of on being taken back to Rustenburg by his parents.

On 6 December 1953, now aged 2 years, he was brought again for examination. The mother stated that he slept badly and often awoke at night, and he was subject to bouts of fever. He drank about 1½ pints of milk a day, but was quite unable to swallow solids; he could not even swallow thin gruel, and when this was offered he vomited immediately. On examination he presented a similar appearance to that on the first occasion. The skull was



Figs. 1 *and* 2. Illustrating dome-shaped skull, broad steep forehead, and median furrow.

dome-shaped and was now 19¼ inches in circumference; it appeared very large compared to the child's puny body. The anterior fontanelle was still open and measured 2×1¾ inches; it did not bulge, it pulsated slightly, and a portion of the metopic suture was palpable. The forehead was broad and steep, with lateral bossing and a median furrow which represented the underlying suture (Figs. 1 and 2).

Control of neck musculature was not normal for his age, but he was able to hold his head erect; in the prone position he experienced difficulty in raising it properly. He could not grip well and could not feed himself. He could only say a few words, and

this not clearly, nor did he understand simple commands addressed to him by his mother in his own language. He had a tendency to shake his head from side to side, and sometimes to make purposeless movements of the hands: he let go as soon as he clasped an object. He could not feed himself, but was able to drink from the bottle without assistance when suitably propped up on cushions. He could not spontaneously rise from a lying to a sitting position, and if placed on his stomach he could not roll over onto his back. The extremities were hypotonic and reflexes were elicited only with difficulty.

After deep sedation with nembutal and full dilatation of the pupils both optic discs were seen to be a little pale but could not be classed as pathological. The child appeared to see quite well, and the pupillary reflexes were normal.

The oral cavity was somewhat small and dentition was somewhat delayed. Both clavicles were palpable.

Urine: No phenylpyruvic acid or other abnormal constituents were detected.

Blood: Kolmer test negative.

Cerebrospinal fluid: Protein 22 mg.%. Globulin Nil. Red blood-cells + (trauma from needle). Kolmer complement fixation test negative. Price precipitation test negative.

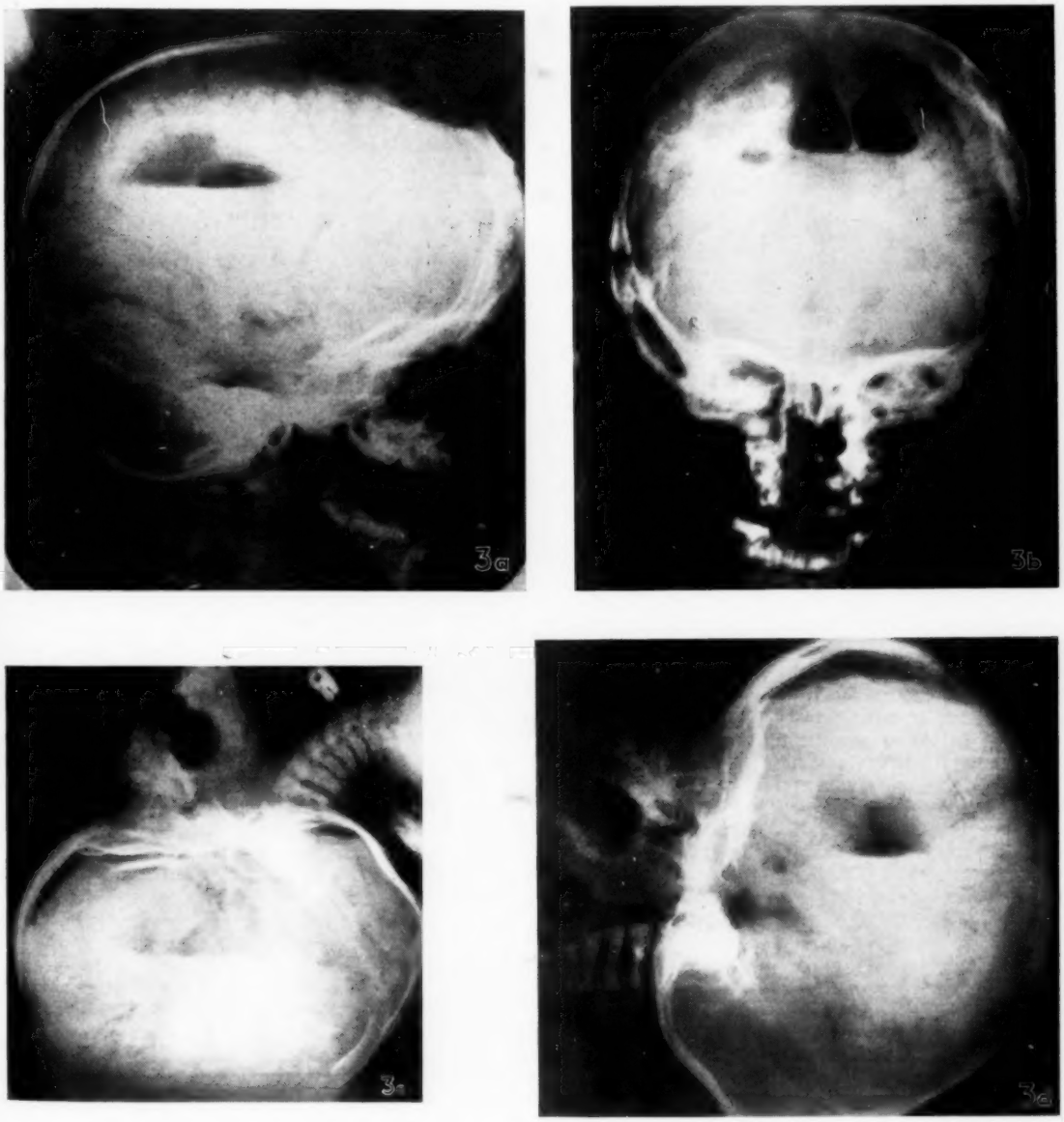


Fig. 3. Air studies, showing atrophy of cerebral gyri. (*a*) Lateral view. (*b*) Antero-posterior view. (*c*) Head inverted. (*d*) Lateral view—supine position with plane of coronal suture in the vertical axis.

Bilateral subdural tap : No fluid obtained.

Air encephalogram : A moderate degree of hydrocephalus was present but there was no distortion of the ventricular system suggesting mechanical obstruction or a tumour. Air could be seen over the cerebral gyri, which appeared to be atrophied (see Fig. 3).

The child was seen again on 30 June 1954. The mother stated that he was not so irritable now, but still did not behave normally. When angry he would knock his head against the wall, and was still inclined to shake his head from side to side. He was now able to chew fairly well and could grip much better. On examination, the circumference of the skull was found to be still 19¼ inches, and the anterior fontanelle still the same size as previously. On grasping, he did not immediately let go as he previously did. He was now able to turn spontaneously from a prone to the supine position, but he could not rise to the standing position unless assisted by pulling his hand. When the hand was held he was able to walk. He recognized close members of the family and was able to say Mamma, Dadda, and the equivalent for 'milk' and 'give'. He was able to sit up spontaneously.

Investigations for Toxoplasmosis. Serological examination for toxoplasmosis was carried out by the Staatliche Medizinal Untersuchungs Amt, Hannover, Germany:

18 January 1954. Child: Sabin-Feldman test positive 1 : 256.
Complement-fixation test negative.
Cadmium-sulphate test ++++.

6 July 1954. Child: Sabin-Feldman test positive 1 : 256.
Complement-fixation test positive ++.
Mother: Sabin-Feldman test positive 1 : 256.
Complement-fixation test positive ++.

Treatment. At one stage the child had an otorrhoea which was treated by an oral suspension of terramycin. At a later stage he developed bouts of fever, associated with upper respiratory infection, and for this he was treated with penicillin and sulphonamide. It is unlikely that he still had any active toxoplasma infection at that stage but, if so, it is possible that the sulphonamide may have limited this.[6]

DISCUSSION ON CASE

It is to be noted that this case did not show any cerebral calcification or chorioretinopathy.

From a serological point of view the case fulfils the criteria laid down by Sabin *et al.*,[7] who state that antibody in a titre of less than 1 : 16 is of doubtful significance. They conclude that the serological diagnosis of congenital toxoplasmosis can be made with the dye-test alone, and it is not necessary to perform a complement-fixation test except during the first few weeks of life, when a child may exhibit a high dye-test titre caused by passive transfer from the mother's blood. However, in the case here recorded the complement-fixation test was in fact positive. As the American workers point out, the complement-fixation test may become positive at a late stage after infection, but it is difficult to explain why it changed from negative to positive so long after the original infection, which must have taken place *in utero*. It does not seem likely that active infection could account for the change in serological reaction, because the dye-test titre remained constant at 1 : 256. Some observers[8] feel that in the absence of any clinical signs one should be a little hesitant of making the diagnosis on serological grounds alone.

The fact that the mother still showed a positive dye-test titre of 1 : 256 accords well with the statement made by the American Committee on Toxoplasmosis[25] that such a titre may persist for 5 years after infection.

EPIDEMIOLOGY

Toxoplasma gondii was first described by Nicolle Manceaux in North African rodents in 1908, but no cases of toxoplasmosis have yet been described in the veterinary literature of South Africa, nor have any unequivocal cases been recognized at post-mortem examination.[9] The histological appearance of sections taken from animals suffering from sarcocystis infection shows a superficial resemblance to toxoplasma infection.[10]

Christiansen and Siim[11] in 1951 demonstrated an infection in hares in Denmark to be serologically identical with that found in human cases. They observed that the sick hares often appeared to be short of breath and after death sometimes exhibited reddish foam in the nostrils. They examined many wild hares found dead in the field or shot in a sick condition, and isolated the parasite by intraperitoneal inoculation into mice. Four strains were isolated and shown to be serologically identical with the human strain R.H. and equally pathogenic. They state that the disease occurs in hares as an acute fatal systemic infection. Slight or subclinical cases are seldom seen and only a few weakly-positive serological reactions have so far been found in control hares. They pointed out a characteristic seasonal incidence, and moot the possibility that the disease may be conveyed by ticks, although mosquitoes cannot be excluded. There appears to be a danger that people handling toxoplasmic hares which have recently died may thus incur infection. In experiments they were able to show that toxoplasma survives for only a short time in the infected tissues, and they warn pregnant women not to clean freshly-shot hares, but only those which have hung for several days, since animals frozen at —30° C did not seem to be infective. Siim also felt, after studying toxoplasmosis in domestic animals, that the dog and possibly the cat may play an important part in transmitting the infection to man, especially in view of the close association between dog and man.

Siim[12] showed that many house-dogs in Copenhagen gave significant positive serological reactions for toxoplasmosis and, as in adult man, the infection in the older dogs might be very mild or even not apparent, but might yet be responsible for spread of infection. In Cincinnati Sabin and Feldman recovered toxoplasma from a pigeon.

Only in laboratory infections has direct transmission of toxoplasmosis from animal to man occurred; in nature the mode of infection is not known. The parasite may gain entry by ingestion or by inhalation or by the mediation of ectoparasites such as ticks. In one case described by Skipper *et al.*[13] the patient was employed in a butcher's shop, where he had probably became contaminated. Serum from his employer gave a positive dye-test to a titre of 1 : 1600, and that of a bitch belonging to this man, and that of a cat which frequented the shop, gave titres of 1 : 93 and 1 : 200 respectively.

Beverley *et al.*[14] have found significantly higher antibody levels in people who have much contact with animals than in the general population. Cases of active infection may have the organisms in the saliva.[15]

CLINICAL MANIFESTATIONS IN MAN

Janku[16] first described the congenital variety in 1923. The disease should be suspected in an infant when the following symptoms occur soon after birth: encephalitis, skin eruption, jaundice, splenomegaly, hepatomegaly, hydrocephalus, chorioretinitis. Instead of hydrocephalus, microcephaly may occur. In later infancy and childhood, convulsions and mental retardation may be found together with the ocular signs, and the latter may cause sufficient disturbance of vision to prevent the child from learning to read. Some cases are for the first time recognized in later childhood by the presence of curvilinear streaks of intracerebral calcification discovered on X-ray examination. Occasionally the congenital type is first recognized later in life by the ophthalmologist. Apparently late-acquired forms of chorioretinitis are not caused by toxoplasmosis. Chorioretinopathy is regarded as a most important sign and may be present at birth or develop a few weeks afterwards. Sometimes the retinal lesions are not observed because they lie so far on the periphery that only with the fullest mydriasis or, in a child, during examination under anaesthesia are they visible.

The severity of the disease probably depends on the period in pregnancy when the infection is passed from the mother to the child. If this occurs in early pregnancy the disease can be so widespread that the child may be born dead. With infection transmitted during late pregnancy, less severe manifestations occur; for instance, there may be no hydrocephalus, microcephaly or cerebral calcification. At a later stage of infancy or childhood, convulsions or psychomotor retardation occur. A mother who gives birth to a child suffering from congenital toxoplasmosis may afterwards have normal children, but the possibility cannot be excluded that quiescent toxoplasmosis in a woman may undergo exacerbation as a result of pregnancy;[17] and toxoplasmosis in successive siblings has been observed.[18]

In the acquired form two main types may be recognized.[13] In the first variety the disease is usually benign and lymphadenopathy is prominent, lasting from 6 weeks to several months. The glands involved are usually in the neck, axillae and groins. Fever occurs at the commencement and does not last very long. In the blood a variable degree of lymphocytosis may occur with occasionally abnormal lymphocytes. Thus the whole picture may resemble that of glandular fever, except that the Paul-Bunnell test is negative and sera give a strongly positive dye-test and complement-fixation test for toxoplasmosis.

The second type of acquired toxoplasmosis is more severe and may be fatal.[19] The illness is typhuslike with high fever, a diffuse maculo-papular eruption, and signs of pneumonia and meningeal irritation or encephalitis. Nerve deafness has been reported.[17] Toxoplasmosis should also be considered in the differential diagnosis of cerebral tumour in children.

Cathie[15] described a case occurring in a 5-year-old boy in London, whose clinical picture simulated glandular fever. The Paul-Bunnell test was negative; and the dye-test was positive 1 : 512, and the complement-fixation test positive 1 : 32. In about 2 weeks the dye-test titre rose to 1 : 1024 and the complement-fixation to 1 : 128. About a month after the first tests were done, sterile blood from the patient was inoculated intraperitoneally into mice and guinea-pigs. After passage the toxoplasma organisms were recovered from peritoneal exudates. Saliva collected from Cathie's patient also yielded toxoplasma on biological examination. Tests showed the strain of organism to be identical with the standard strain. In view of the last discovery Cathie mentions the possibility of transmission of the disease by direct contact from saliva, as for example, in kissing.

SEROLOGICAL DIAGNOSIS

Sabin has devised serological tests; and Warren and Russ[20] have used the complement-fixation method. These tests were devised because recovery of the parasite from human tissues, which would be diagnostic, is rarely successful.

Sabin and Feldman[21] originated a test in which the presence of neutralizing antibodies in a serum is indicated by their effect on the staining properties of toxoplasma parasites. Immune serum and living toxoplasma maintained in the laboratory are allowed to react. When the parasites are then stained with alkaline methylene-blue, the protoplasm of intracellular parasites is unstained and the parasite has a crescentic shape, whereas with normal serum the cytoplasm is darkly stained and the parasites are rounded or oval. With this dye-test these other workers have obtained very high titres in sera from cases of toxoplasmosis. It represents a great advance on earlier tests by virtue of its simplicity. These workers showed that sera which have titres of 1 : 16 or more of the cytoplasm-modifying antibody also exhibit neutralizing properties in the rabbit skin test, which is very reliable, but technically difficult and only possible with fresh serum. It seems that the complement-fixing antibody is different from the cytoplasm-modifying antibody, not only because it may appear later and disappear earlier, but also because sera containing a high titre of the cytoplasm-modifying antibody may be devoid of complement-fixing antibody.

The Sabin-Feldman dye-test has been shown to be very sensitive, and it has been suggested that other protozoa may give rise to cytoplasm-modifying antibodies demonstrable *in vitro* by suitable dye-tests. Muhlpfordt[22] has found that antibodies reacting with toxoplasma in the dye-test were also produced by animals infected with sarcocystis. He concluded that the test can be used in the diagnosis of sarcocystis infections, but that it cannot differentiate between this disease and toxoplasmosis.[23] Michalzik[24] found that the dye-test was also positive in the titre of 1 : 25 in 64% of adult women suffering from infection with *Trichomonas vaginalis*.[23] Thus, whilst the Sabin-Feldman test may be of use in helping to establish the diagnosis of toxoplasmosis, its use is limited by incomplete specificity.[23] On the other hand complement-fixation reactions are entirely specific.

The American Committee on toxoplasmosis[25] holds that active infection is indicated by an 8-fold increase in the titre of the dye-test, to 1 : 256 or more. This

level should be maintained for several weeks, and during this time the complement-fixing antibody should either increase in titre, or if previously negative become positive. The Committee found that a large proportion of the normal adult population in America possesses the cytoplasm-modifying antibody. The incidence increased with age to over 50%, but a titre of 1 : 64 was rarely exceeded. In the Sheffield region of England Beverley and Beattie[26] found that only 2% of the adult population gave a dye-test titre of 1 : 64 and none above that dilution.

The cytoplasm-modifying (dye-test) antibody usually develops within 10-20 days in titres of 1 : 256 to 1 : 4000 or higher, and can persist at these high levels for at least 5 years.[25]

Complement Fixation. The complement-fixation test employs a soluble antigen prepared from toxoplasma-infected chorio-allantoic membranes of chick embryos. As the antigen is stable in the frozen or lyophilized states, testing can be carried out at any time without having to maintain living toxoplasma. The test, alone, cannot be used for diagnostic purposes, because, as stated above,[25] the complement-fixing antibody appears later and disappears much earlier than the cytoplasm-modifying antibody, and may be absent at the height of infection. A negative result therefore does not rule out toxoplasmosis.

Cadmium-Sulphate Test. The cadmium-sulphate test is non-specific and merely indicates an increase in the gamma globulin and albumin content of serum.[27] The positive cadmium-reaction is due mostly to an increase in the gamma-globulin fraction, but an increased content of the alpha (and to a lesser extent of the beta) globulins contributes.[28] The albumin fraction in the serum only precipitates if the globulin fractions are morbidly displaced.

Frenkel[29] stated that the skin test may be negative in both the active and latent forms of toxoplasmosis. A positive reaction is of significance, but Sabin *et al.*[25] conclude that as a diagnostic test it is not valuable.

CLINICAL PATHOLOGY

In toxoplasmosis the histological appearance of glandular material obtained by biopsy does not reveal any characteristic changes, and toxoplasma has not been recognized in the sections. In the peripheral blood abnormal lymphocytes resembling Downey cells, Types I and II, have been seen, but the later cells showed less homogeneous cytoplasm.[13] The Paul-Bunnell reaction is negative in toxoplasmosis. Hyperglobulinaemia may also be present.

SUMMARY

A case of congenital toxoplasmosis is reported in a 2-year-old Indian child born and resident in South Africa.

The child was mentally retarded, the anterior fontanelle was widely opened, and an air-encephalogram showed atrophy of the cerebral cortex. Serological tests for toxoplasmosis were positive in the mother and child.

This is believed to be the first reported case of congenital toxoplasmosis contracted in South Africa where the diagnosis was established during the lifetime of the patient, and points to the possible existence of more cases in this country.

The literature concerning toxoplasmosis is reviewed.

I should like to thank Dr. H. J. Heinz of the South African Institute for Medical Research, Johannesburg, for his valuable advice, and Dr. E. A. Donegan, Pretoria, for his fundoscopic examination. I am also indebted to Messrs. R. P. D. Keogh and Theo Marais for the photographs.

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UNION DEPARTMENT OF HEALTH BULLETIN

Report for the 7 days ended 30 June 1955.

Plague, Smallpox, Typhus Fever: Nil.

Epidemic diseases in Other Countries:

Plague: Nil.

Cholera in Calcutta (India); Chalna, Chittagong, Dacca (Pakistan).

Smallpox in Kabul, Kandahar (Afghanistan); Rangoon (Burma); Allahabad, Bombay, Calcutta, Delhi, Kanpur (India); Chittagong, Dacca, Lahore (Pakistan); Mogadiscio (Somalia).

Typhus Fever in Baghdad (Iraq); Alexandria, Cairo (Egypt).

A STUDY OF 400 CONSECUTIVE MALE BANTU ADMISSIONS TO WESKOPPIES MENTAL HOSPITAL

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Between December 1952 and February 1954 a total number of 400 male Bantu cases were admitted to Weskoppies Mental Hospital on certification. The clinical diagnoses made of these patients are shown in Table I. The proportions of the different diagnostic categories have corresponded fairly well with proportions found in previously published reports on similar groups. It is felt that these 400 cases could be used as a typical cross section of the Bantu male admission pattern found in the general mental hospital, and it is intended to observe them over a period of time in order to determine *their eventual outcome as far as their association with this hospital is concerned.* In this way it might be possible, in a closed group of male Bantu psychotics, to study such factors as 'deterioration', effects of institutionalization, duration of hospitalization, and ultimate prognosis.

TABLE I: CLINICAL DIAGNOSES (WITH PERCENTAGES) OF 400 CONSECUTIVE MALE BANTU CASES ADMITTED BETWEEN DECEMBER 1952 AND FEBRUARY 1954

Diagnostic Category	*Number of Patients*	*Percentage of Total*
Senile and Arterio-sclerotic Psychoses	9	2¼
Cerebral Syphilis	15	3¾
Organic Psychoses due to Drugs, Malnutrition and Infection (i.e. Toxic Psychoses)	73	18¼
Epileptic Psychoses	22	5½
Defective Mental Development ..	15	3¾
Schizophrenic and Paranoid Psychoses	227	56¾
Manic-Depressive Psychoses	28	7
Psychoneuroses	3	¾
All other Psychoses	5	1¼
No Psychiatric Abnormality found on Admission	3	¾
Totals	400	100%

In this series 34 patients are known to have been previously admitted to this or other mental hospitals. One patient was admitted as a 'voluntary boarder', and was subsequently certified as being mentally disordered as defined by the Mental Disorders Act; while another became a voluntary boarder after admission as an ordinarily certified patient. No male Bantu cases were admitted under the legal categories of 'inebriate' or 'temporary' patients. Four cases were, after admission, transferred to another mental hospital for administrative reasons; 3 patients absconded, and were recorded as discharged 'by escape'.

OUTCOME OF CASES

The purpose of this article is to show what has become of these 400 cases by the end of February 1955 as far as their association with this hospital is concerned. This date is one year after the admission of the last case in the series, and 26 months after the admission of the first.

Every case must fall into one or other of the following categories:

(*a*) Still here as certified patients.
(*b*) Died.
(*c*) Discharged from hospital, but since re-admitted, and either subsequently re-discharged or still here.
(*d*) Absconded and discharged 'by escape'.
(*e*) Discharged from hospital and still out.

One must obviously keep in mind the possibility of patients breaking down after discharge, and being admitted to other institutions. There are however only 2 mental hospitals in the Transvaal, and no other organized large-scale facilities for non-European patients. Thus it is most likely that the great majority of patients who break down soon after leaving this hospital are returned here.

In Table II the outcome of the 400 cases (classified by diagnosis) is shown as at May 1954 and February 1955.

A. *Those who are still here*

Of the original 400 cases (Table II) 193 (or 48¼%) were still here as certified patients by May 1954, and 168 (or 42%) by the end of February 1955.

On admission, the organic psychoses formed 35% of the total group and the functional psychoses 65%; and by February 1955 the figures, representing those patients still here, had changed to 29% and 71%.

B. *Those who died*

Of the original group of 400, 28 have died since admission, i.e. 7% (Table II).

Only one of the 9 senile cases has died, but among the 15 cases of G.P.I. there were 6 deaths, all within 8 months of admission.

In the toxi-infective group there were 7 deaths, all but one of whom died within 3 months after admission. Pulmonary tuberculosis was the most frequent cause of death.

Of the 227 schizophrenics in the series, 12 have died. The majority developed lung infections from which they did not recover, despite the use of antibiotics. One case died following electric convulsive therapy (E.C.T.).

C. *Those discharged and subsequently re-admitted*

There are 11 patients in this series who had, at this stage (viz. Feb. 1955), been re-admitted to this hospital after discharge.

Of this number 8 have been subsequently re-discharged, while 3 are still here. The former group con-

TABLE II: 400 MALE BANTU CASES ADMITTED BETWEEN DECEMBER 1952 AND FEBRUARY 1954, GROUPED INTO THEIR DIAGNOSTIC CATEGORIES, IN TERMS OF OUTCOME BY MAY 1954 AND FEBRUARY 1955

Diagnostic Category	Admitted		Still Here			Discharged			Died	
			by May 1954	by February 1955		by May 1954	by February 1955		Number of Patients	
	Number of Patients	Percentage	Number of Patients	Number of Patients	Percentage	Number of Patients	Number of Patients	Percentage of Admissions	by May 1954	by February 1955
Organic Psychoses										
Senile and Arteriosclerotic	9	2¼%	7	6	3½%	2	2	22%	0	1
Cerebral Syphilis (G.P.I.)	15	3¾%	9	9	5¼%	0	0	0%	6	6
Toxic Psychoses	73	18¼%	13	6	3½%	54	60	82%	6	7
Epileptic Psychoses	22	5½%	12	13	7½%	10	9	41%	0	0
Defective Mental Development	15	3¾%	14	13	7½%	1	1	7%	0	1
All Other Psychoses	5	1¼%	2	2	1¼%	2	2	40%	1	1
Totals (Organic Psychoses)	139	±35%	57	49	29%	69	74		13	16
Functional Psychoses										
Schizophrenia:										
Hebephrenic	66	16½%	36	30	18%	28	33		2	3
Catatonic	130	32½%	78	70	42%	46	53		6	7
Paranoid	16	4%	9	8	4¾%	6	7	44%	1	1
Others (unclassified)	11	2¾%	7	6	3½%	4	5		0	0
Paranoid States	4	1%	1	1	½%	2	2		1	1
Manic Depressive Psychoses	28	7%	4	3	1¾%	24	25	90%	0	0
Psychoneuroses	3	¾%	0	0	0%	3	3	100%	0	0
No psychiatric abnormality found on admission	3	¾%	1	1	½%	2	2	67%	0	0
Totals (Functional Psychoses)	261	±65%	136	119	71%	115	130		10	12
Grand Totals	400	100%	193	168	100%	184	204		23	28

sists of 5 manic-depressive (manics), and one case each of schizophrenia, dagga addiction and alcoholic psychosis; while those who are still here are comprised of one epileptic, a schizophrenic, and a case labelled 'toxic psychosis' on his first admission.

When a male Bantu patient is to be discharged from this hospital, a trial period of leave is usually preferred in all the categories except the recovered toxi-infective psychoses. Even if a manic or schizophrenic appears to have recovered completely, trial leave is suggested to the family rather than immediate full discharge. In this way the patient can be brought back, if necessary, without further certification. If, on the other hand, he remains well during the usual 6 months' trial period, he may be discharged completely. One feels that this is a reasonable time for a trial period, for if the patient does not break down overtly in response to his outside environment within this time, it is most likely that he will be able to cope with it to his own individual extent.

It is easier to do this with the Bantu patient than it is with the European, for the former is usually able to return to his previous occupation despite the fact that he is still 'on leave'; whereas the European, who more often returns to a position of responsibility, is frequently unable to reassume his post, unless he has been completely discharged from the operations of the Mental Disorders Act.

D. *Those who absconded*

The legal position as regards 'escape' from a mental hospital is that the patient may be re-taken by the responsible authorities within 42 days after his escape. If the person escaping is not re-taken within this period he must be formally discharged, and before re-admission a new reception order must be made. If, however, the escapee is a 'Governor-General's decision' patient, he may be re-taken at any time after the escape, and brought back to the hospital without any further legal formalities.

Attempts are continually being made by patients to abscond from the hospital. These are unpredictable; they can happen in any diagnostic group; and they may take place very soon after admission, or after many years of detention.

The unsuccessful 'escapee' is often found wandering aimlessly within the hospital grounds, or in the streets near by. At times he manages to reach his home, and is then returned by his family. Occasionally the patient himself will report to a near-by police station, whence he is promptly returned; and often, probably prompted by hunger, or finding himself lost, or for some other unknown reason, the patient will return to the hospital on his own accord after many days of escape.

Of our group, 3 patients made successful escapes. They were all catatonic schizophrenics. Two of the escapees absconded while in the middle of a course of E.C.T., 3 months and 9 months after their respective admissions.

E. *Those who were discharged*

By February 1955, 204 patients out of the original group of 400 had been discharged, and were still 'out' (Table II).

Not a single case of *G.P.I.* had left; all but one of the 15 *mental defectives* were still with us, while only 2 of the 9 *seniles* had been discharged. Both cases were sent out on leave of absence within 6 months after admission, and have remained out.

The *epileptics* were the only group which had increased its numbers since the 'census' of May 1954. This was due to one case on leave of absence who had been re-admitted because of continuous intractable behaviour. The majority of the epileptics who were discharged left hospital within 1 month of admission. Nearly all these cases came in to hospital in states of epileptic furor or post-convulsive confusion, which cleared up within a few days. The epileptic patients who were detained were nearly all 'deteriorated' cases, or were individuals who had committed serious crimes while mentally disordered, and had been subsequently declared 'Governor-General's decision' patients.

The patients labelled *psychoneurotic* or *no psychiatric*

abnormality found on admission did not spend more than 1-4 weeks with us, and only in one case was a Judge's order for further detention requested. The one case who is still here, is a deaf-mute who was sent in as a 'Governor-General's decision' patient. He has not shown any signs of mental disorder since his admission, but he has no family to which he can go, and has become a valuable helper in the ward, in which position he is quite contented.

The 2 cases under the category *all other psychoses* who have been discharged, were a post-encephalitic behaviour-problem case, and a case of post-traumatic aphasia. Neither was certifiable on admission. The two patients in this group who are still here are a case of post-encephalitic dementia and one of post-traumatic dementia.

In the 3 main diagnostic categories the discharge figures were sufficiently large to warrant the use of percentages:

The Schizophrenias and Paranoid States. There were 227 admissions of this group in our series. Of these,

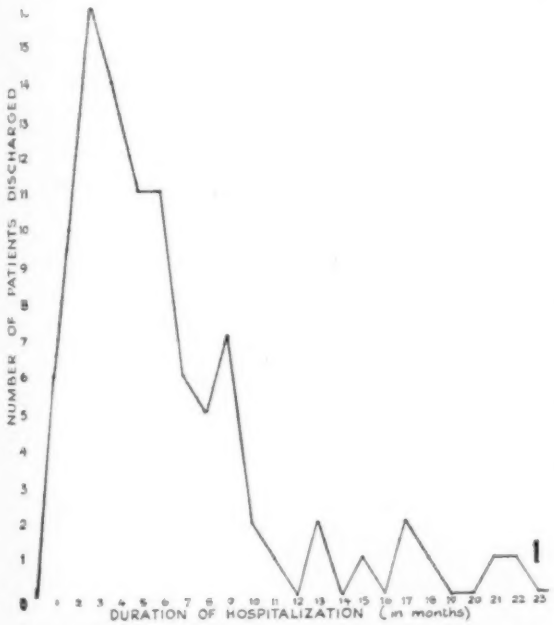

Fig. 1. Graph showing the relationship between the number of schizophrenics discharged and their duration of hospitalization (number of discharges 97).

86 (i.e. 38%) had been discharged by May 1954, and by February 1955 this figure had increased to 100 (44%). Death had occurred in 12 cases (5%), while 115 (51%) are still here. This group of 227 patients was discussed in greater detail in a previous paper.* Of the 97 schizophrenics who have been discharged to date in the usual manner, more than half left the hospital within 4 months after admission. Fig. 1 shows the relationship between the numbers discharged and duration of hospitalization.

The Toxic Psychoses. There were 73 cases in this group. By May 1954, 54 cases (i.e. 74%) had left the hospital, and by February 1955 this figure had increased to 60 (i.e. 82%). By this time death had accounted for 7 cases (10%), while 6 (8%) were still here, of whom 4 are now obviously schizophrenic and the other 2 now show obvious signs of severe organic dementia.

This group of Toxic Psychoses was divided into (*a*) 68 cases where the presenting feature was acute delirium with psychomotor restlessness, and (*b*) 5 cases where the prominent feature was chronic malnutrition associated with signs of mild confusion.

In group (*a*) an etiological factor could usually be ascertained, generally either dagga, alcohol or pellagra. One case had been precipitated by an attack of severe dysentery, while another, who died on the day of admission, was found *post mortem* to have a carcinoma of the liver. A further case in this group was admitted

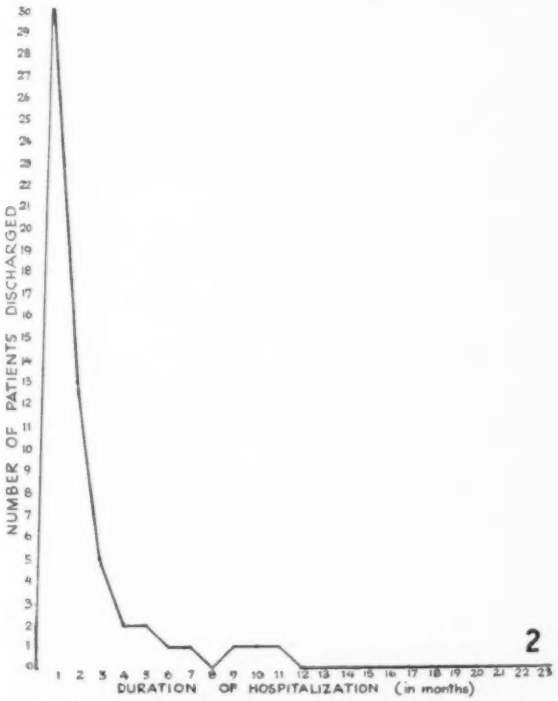

Fig. 2. Graph showing the relationship between the number of cases of acute toxic phychosis discharged and their duration of hospitalization (number of discharges 57).

with frank pulmonary tuberculosis, and he died within a few weeks of admission. Of these acute toxic cases 57 have been discharged, and (Fig. 2) shows the relationship between the numbers discharged and the duration of hospitalization.

In the 5 cases of chronic confusional state—group (*b*)—there was a slow but progressive improvement in

* Moffson, A. (1954): S. Afr. Med. J., **28**, 662.

3, and they were discharged 8, 10 and 10 months after their admission, and by that time were regarded as fully recovered. Of the 2 remaining cases, one is now a typical organic dementia, while the other is now obviously a chronic schizophrenic with 'deterioration'.

The Manic Depressive Psychoses. There were 28 cases in this category. Of these, 26 were manics, and only 2 patients fitted into a clinical picture which in Europeans would have been regarded as that of depression. Whether the Bantu 'depressive' does not get to a mental hospital or whether the 'depressive reaction', as we know it in the European, is uncommon in the Bantu, is a subject of great interest and importance, which still requires elucidation.

This group fared best of all the major diagnostic categories. They suffered no deaths, and nearly 90% of these patients had been discharged by February 1955. The remaining 10% (3 cases) are all chronic manics.

Of the 25 cases discharged, 19 patients left hospital within 5 months after admission.

COMMENTS

(*a*) It appears, in these male Bantu cases, that in the 'functional' mental states, i.e. schizophrenia and the manic depressive psychoses, the discharge rate was highest in the period 3-5 months after admission, and that the chances of a patient leaving hospital after this period, diminished *slowly* with time.

(*b*) In the 'organic' psychoses, however, the discharge rate was at its peak in the first 2 months after admission. After this period the chances of a patient leaving hospital diminished *rapidly* with time.

(*c*) In a few cases, seen a year after the original diagnoses had been made, a change in diagnosis was considered necessary. This usually involved the changing of the diagnosis of hebephrenia to catatonic schizophrenia, and *vice versa;* or a diagnosis of toxic psychosis to that of a schizophrenic psychosis.

SUMMARY AND CONCLUSIONS

A total number of 400 consecutive male Bantu cases were admitted to Weskoppies Mental Hospital between December 1952 and February 1954 under certification.

The outcome of these cases by February 1955, as far as their association with this hospital is concerned, has been investigated.

Of the original number of 400 patients:

168 (i.e. 42%) are still here,
28 (i.e. 7%) have died,
201 (i.e. 50%) have been discharged in the usual manner, and
3 cases (i.e. 1%) have absconded.

The outcome was most favourable in the manic depressive group, and least so amongst the chronic organic dementias.

The axiom that 'the longer the period of hospitalization without improvement, the less favourable the prognosis' could be applied to all the diagnostic categories in this study, and applied especially after 2 months of hospitalization in the organic-psychosis group, and after 5 months in the functional-psychosis group.

I wish to thank Dr. I. R. Vermooten, Commissioner for Mental Hygiene, for his perusal, comments, and permission for publication of this paper. I am also grateful to Dr. B. P. Pienaar, Physician-Superintendent of Weskoppies Hospital, for the use of the case material in this study.

RUMINATION IN A BANTU BABY *

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A review of the literature on rumination in infancy might suggest that the condition was extremely rare. Gruleë[1] stated that, so far as he was able to find, the first reported cases came from Freund[2] in 1903, who recorded a small number of cases which he regarded as being closely related to pylorospasm but gave no definite findings. Between 1906 and 1915 16 cases were reported, mostly in German literature quoted by Gruleë.[1] The youngest child in this series was 13 weeks old. In 1917 Gruleë[1] reported on 6 cases which he had observed over a period of 3 years and which brought the number of reported cases to 22. Since then no further cases have been reported. No reported case, so far as I have been able to ascertain, occurred in a non-European infant or at such an early age as the case here reported.

That the condition is not so rare as the paucity of reports would suggest is evident from the fact that most paediatricians have encountered one or more cases in the course of practice but have not thought them to be of sufficient interest or importance to warrant publication. When, however, it is realized that the mortality rate is 25% and in severe cases may be as high as 50%, and that the condition is definitely characteristic and therefore easily recognizable, it seems desirable to report the present case.

CASE REPORT

P., a male Bantu baby aged 5 weeks, was transferred to the paediatric ward, Baragwanath Hospital, on 11 March 1951. He had been admitted a few days previously as a lodger baby with his mother, who was then suffering from severe diarrhoea and anaemia and later developed thrombophlebitis. She complained that the baby was not getting enough food and it was noted then that his weight was only 5½ lbs., and that he looked thin and under-nourished.

* A paper presented at the 1st South African Paediatric Congress, Durban, 1953.

He was the 4th baby; the first 2 were alive and well; the 3rd baby died one day after birth, cause unknown. Throughout her pregnancy the mother experienced pain in the right iliac fossa, but was otherwise well. After a normal labour she managed her own delivery at home; the baby appeared healthy at birth and had progressed satisfactorily until she was hospitalized, too ill to nurse him. He had been breast-fed and had not vomited.

On examination, I found a restless, tense, apathetic and undernourished baby and, in between crying, he would put his fist into his mouth and suck vigorously, thus managing to swallow a considerable amount of air. At the same time, he would throw his head back and hyper-extend the spine. The rest of the clinical examination was negative.

Three days after his transfer the first episode occurred. After a feed, the child made a gurgling sound, choked, started gasping for breath and became cyanosed; the mouth was found to be full of vomitus, which was sucked out and continuous oxygen administered. The child improved after this and, for almost a month, apart from a failure to thrive in spite of an adequate diet, nothing definite was recorded. During this time investigations were carried out in order to determine the cause of this failure to thrive. The Eagle blood-test was negative, the tuberculin tests 1 in 1,000 and 1 in 100 were negative. Blood counts were within normal limits. The stools looked normal and no pathogenic organisms were grown on several cultures. Subdural taps were negative.

On 11 April, 1 month after admission, the following progress note was recorded: Child still wasted; general condition unsatisfactory; no weight gain in spite of taking feeds well; small vomits have occurred after feeds—the vomitus gushes up through the nose and is accompanied by coughing. The following day it was noted that the child was pyrexial and, on examination, the throat was found to be injected and crepitations were heard at the right base behind. X-ray showed slight changes in the right lower lobe suggestive of pneumonitis, which was probably an aspiration phenomenon.

A day or two later, while on the ward round, I happened to be watching the child from behind. He had been fed, and I noticed he was making a chewing movement with his jaws with the tongue extruded. After a short while he put his fist into his mouth and started sucking vigorously, throwing his head back and hyperextending the spine. The facial expression during all this was one of anxious determination, to change a few seconds later to one of pleasurable achievement as the vomitus trickled out of his nose and mouth (see Fig. 1). The whole procedure had been so characteristic that I felt certain we were dealing with a ruminator. Having made the diagnosis and with a view to exhibiting some rational form of therapy, I decided to try and explain the mechanism by which these infants can regurgitate their food at will.

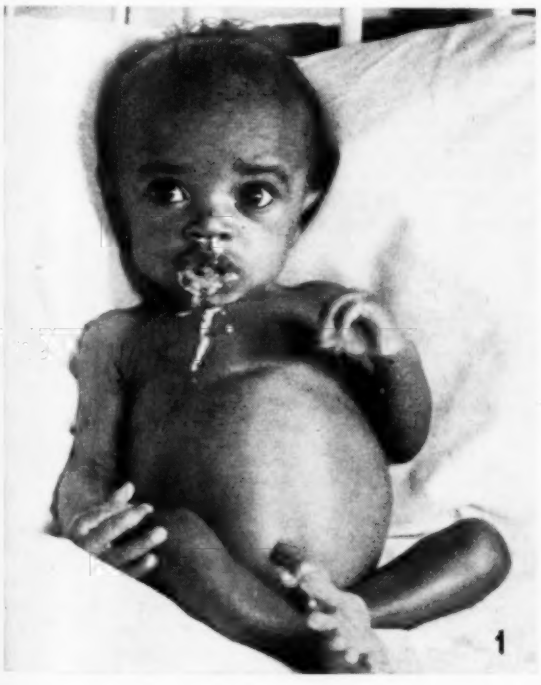

Fig. 1

Before describing the investigations carried out, I would like to mention briefly what various authors have suggested as possible aetiological factors and to remind you of the various forms of therapy that have been suggested. Mitchell Nelson states that the cause is unknown but that it is believed to be a neurotic disorder. Williamson thinks that it is functional but that it may result, in the first instance, from an overfilled stomach (the exciting factor). Thompson and Finlay refer to it as one of the most characteristic 'bad habits' of early infancy; in some babies it lasts but a short time and does little harm, in others it is severe and persistent and has a serious effect on the nutritional status. Griffith Mitchell observes that it has been considered to be a nervous condition; that its production may be associated with dilatation of the stomach and swallowing of air; and that sometimes it has been preceded by pylorospasm. Sheldon puts it that the cause of this curious condition is unknown but suggests that the habit is formed from the possetting of a little milk which so commonly happens with infants who are over-fed or who are air-swallowers. Holt and Howland consider it to be dependent upon a reflex irritability of the organ. Pearson and Wylie suggest that rumination may, as with most stereotyped nervous habits, be predisposed to by some pre-existing local condition, commonly air-swallowing and dyspepsia. Garrod, Batten, Thursfield and Paterson graphically describe the whole process but make no mention of the underlying pathology; it is interesting to note that they state that the condition never occurs before the 4th month.

The numerous methods of treatment, which are itemized below, lend confirmation to the fact that, as yet, no definite mechanism has been demonstrated to explain the cause of this distressing habit:

1. Thickening the feeds. In the past many substances have been used for this purpose; recently Professor Lelong of Paris has advocated the use of carob flour and claims to have had good results.
2. Feeding with buttermilk.
3. Feeding with alkalinized kafer.
4. Plugging the nostrils.
5. Strapping up the chin.
6. Splinting the arms in order to prevent the baby from sucking its hands.
7. Washing out the stomach and feeding by gavage.
8. The use of cocaine or other local anaesthetic applied to the throat, oesophagus and stomach.
9. Sedation with chloral or bromide or both, before meals.
10. Distracting the baby's attention after feeds by hanging up bright toys or bells in the cot and otherwise amusing it.
11. Erect positioning of the child after feeding, etc.

The association of pylorospasm has been described in too large a proportion of cases to be of no significance.

Gruleë came to the conclusion that there is a general tendency in ruminators towards overaction of the involuntary circular muscles, with the primary action in the stomach, excited by pylorospasm (the term being used in a wide sense), resulting in the food being forced back into the oesophagus and held there by the over-action of the muscles of the lower end of the oesophagus (pharyngospasm), thus enabling rumination to proceed until these muscles relax.

Hess[3] in his article on the pylorus, pylorospasm, and allied spasm in infants (1914), recorded some very interesting observations. By passing special catheters, he was able to demonstrate, at or soon after birth, what he called true congenital pharyngospasm, cardiospasm and pylorospasm, while similar spastic conditions might be met with during the neonatal period, having been excited by post-natal intercurrent factors—commonly gastric disturbances and, in particular, dyspepsia. From this it would seem that in some neonates there is a congenital tendency to spasm of the sphincters and that, clinically, this tendency may remain entirely latent or manifest itself in some slight disturbance such as occasional vomiting, sometimes projectile, or may only become evident in one form or another following a super-imposed exciting factor, namely dyspepsia or aerophagy. If we apply these observations to rumination one may postulate that the initial vomiting is precipitated by this exciting factor, usually a gastric disturbance such as over-feeding or air-swallowing in a baby with the congenital tendency to sphincteric spasm; and because of the pleasure derived from it, as evidenced by the facial expression, a habit soon becomes established and the rumination voluntary. This is further suggested by the fact that, almost without exception, the ruminator is a spastic hyperkinetic type of infant; it is restless, cries constantly, and is extremely interested in its surroundings. Moncrief refers to rumination as one of the psychosomatic problems of the hyperkinetic child.

INVESTIGATION

Having then postulated a mechanism by which this condition is precipitated and perpetuated, we decided to try and demonstrate it radiologically by screening the infant during a barium meal and taking serial pictures. This was done by two independent workers, Dr. Margaret Findlay, then Head of the Department of Radiology, and Dr. Paul Marchand, who was attached to the Thoracic Unit (Baragwanath Hospital).

It is said, and must be remembered when interpreting the results, that the ruminating habit is not indulged in when anyone is observing the child—let alone during the ordeal of a radiological examination. Nevertheless some interesting observations were recorded.

On 28 May 1951, Dr. Marchand screened the child and reported as follows:

> The child sucked vigorously at the barium milk emulsion. In the erect position, the barium passed rapidly to the level of the aoticarch and then on into the stomach, showing a vigorous normal, primary peristaltic wave, but a certain amount remained unevacuated in the oesophagus and stimulated rapid deep and forcible secondary waves, which immediately cleared the remaining barium from the oesophagus. There was no evidence of any hold-up at the cardia. While in the supine position the child was made to suck continuously at the bottle. The primary peristaltic wave was much the same as in the erect position. Once the initial barium mass had entered the stomach, a considerable amount remained in the oesophagus. The bottle was then removed and the screening continued. There were deep and vigorous secondary waves observed which, however, appeared uncoordinated. They would advance from the level of the aotic arch for about an inch or two, and would then reverse to form an anti-peristaltic wave forcing the barium back towards the aotic arch, at which level the waves became antegrade once more. This process was repeated several times, giving a see-saw motion until, quite suddenly, the antegrade wave continued uninterrupted into the stomach. At the same time rapid shallow tertiary waves were observed, which is quite an unusual phenomenon in an infant and their significance not clear. The appearances are those of a hyperkinetic oesophagus showing signs or uncoordinated muscular activity.

Because of this, Dr. Marchand decided to repeat the observations and on 14 June 1951 he reported as follows:

> The child sucked vigorously throughout the examination. In the erect position the barium passed rapidly into the stomach and it was difficult to visualize details of oesophageal movements, but reversed peristalsis was not seen on this occasion. In the supine position the barium passed rapidly into the thoracic stomach, although there was a slight delay at the level of the diaphragm. Deep secondary peristaltic waves could be seen arising at the level of the aotic arch. These passed slowly down the oesophagus, and every third wave or so would continue along the whole length of the oesophagus and empty its contents into the stomach. The other waves, as they approached the lower end of the oesophagus, would slow down and eventually stop about 1 inch above the level of the diaphragm. A spasm at this level would persist momentarily, ballooning out the supra-diaphragmatic portion of the oesophagus in the manner of a phrenic ampulla. Suddenly it would relax and the barium contents in the dilated portion would flow in a retrograde manner as if tension had suddenly been relaxed, giving rise to a see-saw movement. This process would continue until the antegrade wave would pass, without any apparent difficulty, into the stomach. The barium, having entered the stomach, remained there throughout the examination, which lasted about 10 minutes. At the end of this time only traces of barium had entered the duodenum. Posture had only a slight effect in hastening gastric emptying. The signs point to pyloric spasm.

On 27 June 1951 Dr. Findlay carried out the third examination and reported as follows:

> Screening examination was carried out while baby was sucking a barium milk mixture. In the erect position the mixture passed readily into the stomach and no abnormal oesophageal waves could be seen. In the supine position there was some delay at the cardia. This was followed by secondary waves of contraction, commencing at about the level of the aotic arch, passing down the oesophagus, and sometimes emptying its contents into the stomach. At other times there would be a hold-up at the cardia with a suggestion of reversed peristalsis. Throughout this examination barium was not seen to pass through the pylorus and, when in the prone position, only a small quantity of barium had passed through the pylorus after a period of 10 minutes. In the radiograms taken about 15 minutes later practically no barium was demonstrated in the oesophagus. Initially there was undoubtedly a period of pylorospasm, and radiograms taken the next day during vigorous sucking of the barium mixture in the left posterior oblique position demonstrated a filled oesophagus, suggesting some delay at the cardia.

These examinations, I think, have shown quite clearly that spasm, either cardiac or pyloric or both (as in this case), is the primary underlying aetiological factor and that this primary spasm initiates secondary anti-peristaltic waves which were responsible for the food being

regurgitated in a manner characteristic of the ruminator. This being the case, it appeared to me that a rational therapeutic approach would be to exhibit an antispasmodic. The infant was therefore given 2 drops of a 1-in-100 alcoholic solution of Eumydrin (atropine methyl nitrate) 20 minutes before each feed. The response was almost dramatic. The regurgitation ceased and the child began to put on weight for the first time since admission. The Eumydrin was continued for 14 days and then gradually withdrawn, and thereafter, apart from an occasional episode, the child continued to make satisfactory progress and, when discharged some 3 weeks later, was taking its feeds well and remained in a satisfactory condition. When seen 3 months later it was still doing well.

I have tried to give you a clinical description of a case of rumination in a 9-week-old Bantu baby which was seriously affecting the child's nutritional status, and have suggested that the primary aetiological factor is one of spasm in a hyperkinetic infant with a congenital predisposition to spasm excited by some gastric disturbance, in this case air-swallowing, which initiates secondary anti-peristaltic waves by which the child is able to regurgitate its food at will. Although the exhibition of an antispasmodic was followed by satisfactory response, recent personal experience in the treatment of further cases shows that the combination of a sedative with the antispasmodic has an even greater value.

SUMMARY

A case of rumination in a Bantu baby is described.

It is suggested that the primary aetiological factor is spasm—either pharyngospasm, cardiospasm or pylorospasm or a combination of these.

Certain babies, usually of the hyperkinetic type, have a congenital tendency to spasm which may manifest itself at or soon after birth or remain latent until some post-natal intercurrent factor, usually dyspepsia or aerophagy, excites it. Once this spasm is established, it initiates secondary anti-peristaltic waves which enable the child to regurgitate its food. As a result of the pleasure derived, it soon becomes a voluntary habit.

The antispasmodic Eumydrin was exhibited with a dramatic response, but in the light of more recent experience its combination with a sedative is advised.

REFERENCES

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3. Hess, Amer. J. Dis. Child., **7**, 184.

IN MEMORIAM

DR. THOMAS JONES

The death took place in Pinelands, Cape, on 13 June 1955 of Dr. Thomas Jones, aged 80 years.

Born in Carmarthen, Wales, Dr. Jones qualified at the Middlesex Hospital, London, after which he practised in London in partnership with his brother for some years. Then, owing to ill health, he left England and became a ship's surgeon. He remained at sea for three years, during which time he visited many ports of the world.

Dr. Thomas Jones

In 1901-1902 he settled in South Africa and practised in Graaff-Reinet, Middelburg, Cape (where he was associated in practice with Dr. Henry Jones, whose daughter he married), Rosmead and Naauwpoort till 1924; he then came to Cape Town, practising first in Parow and then in the Gardens until 1936. He was a Railway Medical Officer for 33 years, and after retiring from the service he acted as Medical Officer at Langa Native Location until his final retirement from practice.

Dr. Jones is survived by his widow, son (Dr. T. H. L. Jones) and 4 daughters, of whom one (Dr. Megan Jones) followed her father's profession (and is also the wife of a medical man) and two others married members of the profession.

Dr. P. T. Cairns, of Maitland, Cape, writes: Being conscious of the modern trend in medical practice one thinks back to the general practitioner of 50 years ago. He is a slowly disappearing entity, replaceable, but alas, being replaced in small, very small, numbers—a surgeon who knew his limitations, an obstetrician of sound judgment developed by many a midnight vigil, often in the poorest houses, and a physician whose patient and the whole family were not only his medical care but the subject of his solicitude extended to their personal aims and aspirations.

Such a general practitioner was Dr. Thomas Jones, whose death has recently taken place. I can speak warmly of his many good qualities. Ever unobtrusive, seeking no publicity, courteous and a grand, upright, honourable colleague, we his friends mourn his loss.

PASSING EVENTS : IN DIE VERBYGAAN

Erratum. In the list of medical degrees conferred at the University of Cape Town on 24 June 1955 and published in the *Journal* on 2 July, the degree of Master of Surgery (Otorhinolaryngology) conferred on Dr. Jack De Villiers, M.B., Ch.B. should have appeared under the heading Ch.M.

The Cape Town Branch of the South African Society of Obstetricians and Gynaecologists. The Committee of the Branch, appointed in March 1955, consists of the following: Dr. J. C. Coetzee (Chairman), Dr. E. M. Sandler (Secretary), Dr. T. St. V. Buss and Dr. Glyn Rees.

Ciba Foundation's Awards for 1954-55 for research relevant to the problems of ageing. The panel of referees has considered 51 papers from 17 countries and the following awards have been made (the names of the leading authors only are given): £400 to S. M. Friedman (University of British Columbia); £250 each to E. M. Hartsook (Pennsylvania State University), M. M. Hoffman (McGill University), J. E. Lovelock (National Institute Medical Research, London) and H. Sobel (Cedars of Lebanon Hospital, Los Angeles); £100 each to W. Hobson (Sheffield University) and E. Geiringer (Glasgow Hospital for Sick Children). The conditions for the 1955-56 award will be announced shortly.

CORRESPONDENCE : BRIEWERUBRIEK

COENURUS CEREBRALIS IN THE HUMAN BRAIN

To the Editor: Recently a Native woman was admitted to hospital under my care. She complained of pains all over the body and of severe headache. She exhibited photophobia and on occasions mentioned 'cloudy vision'.

Except for a slight rise of temperature on the 3rd day after admission she was apyrexial during the 6 days she spent in hospital. She died suddenly on the 6th day and an autopsy was performed. Several small cysts were discovered in various areas of the cerebrum and in the cerebellum, chiefly in the floor of the 4th ventricle. Just behind the optic chiasma there was a thin-walled cyst about the size of a pea. Several of these cysts were sent to the laboratory and the following report came back:

Brain: Coenurus cerebralis. Brain showing several parasitic cysts. No definite hooklets have been seen. This is the bladder-worm stage of the dog tapeworm. *Multiceps multiceps.* This stage in sheep causes 'the gids'. References to this condition may be found in *The Lancet*, 4 August 1951, p. 198, and 29 December 1951, p. 1202.

The patient presented a picture of encephalitis. The cerebrospinal fluid was under considerable pressure but the laboratory reported nothing abnormal in the fluid.

Any comments on this case would be most interesting. Perhaps you would be good enough to indicate the incidence of similar cases in this country.

F. A. van Heerden

Bergville, Natal
24 June 1955.

TREATMENT OF PRURITUS ANI

To the Editor: Dr. Lennox Gordon's letter[1] is of value in that it again brings before the profession a useful method of treatment. While his advice to wash may not figure in surgical text-books, it has long been advocated as standard practice by dermatologists.[2, 3] Whether or not soap is always of value is a debatable point and, in my own experience, I would say that at least as much benefit can be obtained from the use of plain water, particularly if it is employed immediately after defaecation. The simplest way of doing this is for the patient to take to the toilet a towelling face cloth, one corner of which has been moistened. The moistened area is then used to cleanse the anus and the rest of the towel to dry it. This suffices to control many cases, but where it fails, the application of Benadryl cream after defaecation, and during spasms of itching, is of value.

Where irritation is acute and there is much swelling, bed rest and wet dressings are indicated. Of these, the most useful is 0·003% gentian violet in calamine lotion. This apparently homoeopathic concentration of gentian violet is, in practice, sufficient to control bacterial and monilial infection, provided the lotion is applied with such frequency as to prevent the compresses drying out.

Where wet dressings are impracticable, Cortogen F cream should be tried. It is important to stress that a cream containing hydrocortisone rather than an ointment should be prescribed. Greasy ointment bases are inimical to improvement.

Once the acute phase has passed, and in cases presenting originally with sub-acute or chronic symptoms, radiotherapy is of great value.

These methods, however, are indicated only when no other aetiological factors can be found. When threadworms and such are present they demand appropriate action—and here a word (or two) is necessary on the importance of antibiotics, which are fast establishing themselves as the commonest cause of pruritus ani. Whether because they produce conditions favouring the unrestricted proliferation of yeasts such as *Candida albicans* or of bacteria such as *Staphylococcus aureus*, *Proteus* and *Pseudomonas*, or because they act in some other way, is not material;[4] by some means or other they are responsible and, in addition, they appear to have increased the incidence of black tongue, perlèche, cheilitis, glossitis and vulvovaginitis, and to have produced occasional cases of generalized moniliasis and fatal post-operative enteritis.[5] A caution regarding their indiscriminate use is therefore essential. Manufacturers are aware of these dangers and one has recently marketed a specific substance* to cope with monilial overgrowth, while another has combined his product with a group of vitamins.† From the selfish point of view of one who has twice had pruritus from the necessary use of their products I wish their endeavours every success.

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29 June 1955

* Mycostatin (Squibb).
† Terramycin S. F. (Pfizer).

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2. Sulzberger, M. and Wolf, J. (1952): *Dermatology, Essentials of Diagnosis and Treatment*, p. 451. Chicago: Year Book Publishers Inc.
3. Andrews, G. (1946): *Diseases of the Skin*, p. 78. Philadelphia: W. B. Saunders Co.
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TRANSFERRED HYPNOTIC SUGGESTION IN THE RELIEF OF ASTHMA

To the Editor: One of the obstacles preventing the relief of patients in an attack of bronchial asthma by means of hypnosis, without the use of drugs, is that the attacks occur at any time of the day or night and the medical hypnotist cannot always be present. To overcome this it would be necessary to transfer the hypnotic control of the patient from the medical hypnotist to someone who is in daily contact with the patient, e.g. father, mother, wife or brother.

I have just tried this method in a boy aged 13 years who has been suffering from bronchial asthma for the past 9 years, his house doctor having to come in regularly to give him intravenous aminophyllin and intramuscular adrenalin to relieve him of his attacks, which wore down not only the boy but also members of the household who had to witness the attacks.

I hypnotized the boy, light-stage hypnosis being achieved, in the presence of his father. I then gave the boy a post-hypnotic command that whenever his father told him to go to sleep and relax it would be the same as when I told him to go to sleep and relax. With this method it has not been necessary for the boy to have any antispasmodic drugs or injections. Whenever the father sees that he looks tired and has a slight wheeze he gives him the post-hypnotic command of 'sleep'. The boy immediately goes into a light stage of hypnosis and is relieved of the impending attack. He is now putting on weight, eating his food and taking more interest in his school work.

I think that this method could be satisfactorily used in such conditions as psychosomatic migraine and dysmenorrhoea.

S. Kaimowitz

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3 June 1955